CYCLOADDITIONS IN ORGANIC SYNTHESIS: DEVELOPMENT AND APPLICATION OF NEW METHODS FOR CONSTRUCTING POLYCYCLIC AROMATIC SYSTEMS

by

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Honors B.S., Saint Louis University (1989)

SUBMITTED TO THE DEPARTMENT OF
CHEMISTRY IN PARTIAL
FULFILLMENT OF THE
REQUIREMENTS FOR THE
DEGREE OF

DOCTOR OF PHILOSOPHY

at the

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

May 1994

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ACKNOWLEDGMENTS

By no means should the work described in this thesis be interpreted solely as the accomplishments of one individual. Many people have assisted me in completing this portion of my education. A good deal of credit for my professional development belongs to Rick Danheiser. By displaying strong teaching and research qualities, Rick has helped me to define my own style as a chemist, and for this I am very grateful. I am also indebted to Vincent Spaziano for providing me with the opportunity to conduct research as an undergraduate at Saint Louis University; it was this two-year experience that ignited my interest in organic chemistry. Bruce Kowert, Harold Dieck, and the rest of the chemistry faculty at SLU also deserve my thanks for their efforts to enlighten a sometimes lackadaisical mind.

Several former group members, including Brian Dixon, Eric Stoner, Ray Miller, and Jill Netka, were in large part responsible for easing my transition from college to graduate school. These people were invaluable as mentors, but their friendship was probably more important. Len McMullen, Roberto Fernandez, and Susy Allemann, three post-doctoral fellows in our lab, provided advise about writing a thesis and finding a job which proved to be invaluable over the past 18 months.

I would like to thank all of the current members of the group, as well as offer a blanket apology to those who may have been put off by my strange personality. It has been my pleasure to have worked with Annie Helgason for the past 4 1/2 years. She has proven to be a constant source of encouragement, ideas, and laughs (that is, when she was not falling asleep in group meeting). Brian Bronk (a good friend, sometimes carpool partner, and fellow traffic cone) tended to bring out the demented side of me, usually to the chagrin of those within earshot. In the odd serious moment, however, he proved to be one of the brightest chemist I have known. I am indebted to Jennifer Loebach for her ideas, patience, and unique (but decidedly Midwestern) outlook on life. Her friendship and sense of humor helped to make graduate school a more enjoyable experience. Alex Huboux provided helpful discussions and friendly banter, but I wish someone had confiscated his collection of dance music tapes. Kathy Lee tried to keep some semblance of order in our labs, often against overwhelming odds. She was always willing to offer help and friendship, and I am very grateful to her.

I must thank Sandy Gould for contributing significantly to my graduate work and for being a good friend. Not only did she help to synthesize some of the materials for the azulene project, but she also was in large part responsible for the discovery of the enyne cycloaddition described in Part II of this thesis. Her accomplishments are remarkable given that most of her equipment and glassware somehow wound up in my possession. It is amazing to me that she has remained sane over the past 1 1/2 years, since most of that time she was forced to endure the rantings of her lab partner. I consider myself fortunate for having shared a bay with her.

The future of these laboratories seem to be in good hands, with the likes of Mike (Ulf) Lawlor, Rob (next slide, please) Niger, and Brenda Gacek warming up in the bullpen. Mike's unfortunate taste in hockey teams aside, he has proven to be a good friend for the year that I have known him. Rob is probably the strangest person I have ever encountered, but he has made the past year interesting and enjoyable. I must also thank Adam Renslo and Melanie Bartow for the contributions which they have made to this thesis. Finally, thanks to Brian Bronk, Jennifer Loebach, and Sandy Gould for proof reading this thesis, and to all of my Toxic Waste teammates (softball, hockey, volleyball) for providing entertainment and beer.

For Kathy

CYCLOADDITIONS IN ORGANIC SYNTHESIS: DEVELOPMENT AND APPLICATION OF NEW METHODS FOR CONSTRUCTING POLYCYCLIC AROMATIC SYSTEMS

by

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Submitted to the Department of Chemistry
on May 17, 1994 in partial fulfillment of the
requirements for the Degree of Doctor of Philosophy

ABSTRACT

A new synthesis of substituted azulenes via metal-catalyzed reaction of 4-aryl-4-bromo-1-diazo-2-butanones has been developed. Regioselective ring expansion-annulation of these diazo ketones occurred at room temperature upon treatment with a catalytic amount of a rhodium(II) carboxylate followed by base (4-dimethylaminopyridine) and a trapping reagent (e.g. acetic anhydride). The products of this annulation process are 1-hydroxyazulenes which, when suitably functionalized, can be elaborated via transition metal-mediated cross coupling reactions. Utilizing this method, the synthesis of the anti-ulcerative *Azuletil sodium* has been achieved.

Synthetic approaches to the naturally-occurring phenalenone diterpene salvilenone have been investigated. Initial exploration of a synthetic route which relies upon an intramolecular [4+2] cycloaddition reaction between conjugated enynes and acetylenes as the key step has been examined. Several model systems for this reaction have been studied.

Thesis Supervisor: Rick L. Danheiser

Title: Professor of Chemistry

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Part I

A New Synthesis of Substituted Azulenes

CHAPTER 1

Introduction and Background

The azulenes constitute the best known class of polycyclic non-benzenoid aromatics.[1] Since their discovery in the mid-nineteenth century, this class of compounds has generated interest among chemists due to their beautiful colors, interesting reactivity, and potential commercial applications. Most of the early reports of azulenes are found in the literature of essential oil chemistry; Piesse's report in 1863 was among the first.[2] Conventional wisdom of the day held that this compound was most likely a copper derivative; however, because of the volatility of this material, doubt was cast on this supposition. In spite of the considerable effort of numerous researchers,[3] it would be seventy years before the proper structure for Piesse's azulene was determined.

In 1915, Sherndal provided a clue to the structure of Piesse's azulene when he determined that this blue material could be extracted into aqueous solutions with mineral acid to provide a yellow-brown solution. The blue compound could then be regenerated by dilution of the acid layer with water.[4] This procedure allowed access to material of

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[1]Reviews: (a) Zeller, K.-P. in *Methoden der Organischen Chemie (Houben-Weyl);* Kropf, H., Ed.; Georg Thieme Verlag: Stuttgart, 1985, Vol. V/2c, p 127. (b) Lloyd, D. *Nonbenzenoid Conjugated Carbocyclic Compounds*; Elsevier: Amsterdam, 1984; pp 352-377. (c) Lloyd, D. *The Chemistry of Conjugated Cyclic Compounds*; John Wiley and Sons: Chichester, 1989; Chapter 13. (d) Mochalin, V. B.; Porshnev, Yu. N. Russ. *Chem. Rev.* **1977**, *46*, 530. (e) Gordon, M. *Chem. Rev.* **1952**, *50*, 127. (f) Porshnev, Yu. N.; Mochalin, V. B.; Cherkashin, M. I. *Russ. Chem. Rev.* **1982**, *51*, 1089. (g) Becker, D. A., Ph.D. Thesis, Massachusetts Institute of Technology, 1988.

[2]Piesse, D. *Compt. Rend.* **1863**, *57*, 1016.

[3](a) Hentzschel, W.; Wislicenus, J. *Annalen* **1893**, *275*, 312. (b) Barbier, P.; Bouveault, L. *Compt. Rend.* **1894**, *119*, 281. (c) Wallach, O.; Tuttle, E. F. *Annalen* **1894**, *279*, 397. (d) Sabatier, P.; Mailhe, A. *Compt. Rend.* **1914**, *158*, 985. (e) Kremers, R. E. *J. Am. Chem. Soc.* **1923**, *45*, 717. (f) Ruzicka, L.; Rudolph, E. A. *Helv. Chim. Acta* **1926**, *9*, 118.

[4]Sherndal, A. E. *J. Am. Chem. Soc.* **1915**, *37*, 167, 1537.

sufficient purity that elemental analysis and molecular weight determinations could be made. These measurements provided a striking conclusion; Piesse's azulene contained only carbon and hydrogen and has an empirical formula of $C_{15}H_{18}$! In 1936, Pfau and Plattner, using the experimental evidence of Sherndal and the relatively new theory of aromaticity,[5,6] correctly assigned the structure of Piesse's azulene (known today as guaiazulene); furthermore, they were able to validate their proposal by the synthesis of a blue hydrocarbon which possessed the azulene nucleus.[7]

Why Is Azulene Blue?

One of the most distinguishing features of azulenes is their intense color. Guaiazulene is an intense blue substance, but not all azulenes are limited to this color. Both naturally occurring and synthetic azulene derivatives have colors ranging from red to violet, depending upon the nature and position of the substituents incorporated in the molecule. This phenomenon is demonstrated below for alkyl-substituted azulenes. For azulene, the electronic transition in the visible spectrum responsible for azulene's blue color occurs at 580 nm.[1b] The incorporation of substituents into the azulene system, however, changes the energy of this transition, either increasing or decreasing the wavelength of the color-determining absorption.[1b] Unlike other aromatic systems, the inclusion of an alkyl group does not necessarily lead to a bathochromic shift in the visible spectrum.[1b] In fact, the site of substitution is the determining factor for the shift in the 580 nm band. This rule also holds for polyalkylazulenes (i.e. the values are additive), but it does not extend to other functionality.

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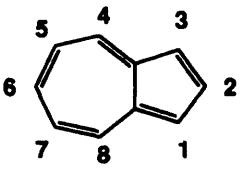
[5]Armit, J. W.; Robinson, R. *J. Chem. Soc.* **1925**, *127*, 1604.
[6]Huckel, E. *Z. Physik.* **1931**, *70*, 204; **1931**, *72*, 310.
[7]Pfau, P.; Plattner, Pl. *Helv. Chim. Acta* **1936**, *19*, 858.

Figure 1



Position	Δ (nm)
1	+35
2	-20
3	+35
4	-15
5	+15
6	-15
7	+15
8	-15

Effect of Alkyl Substitution on the 580 nm band

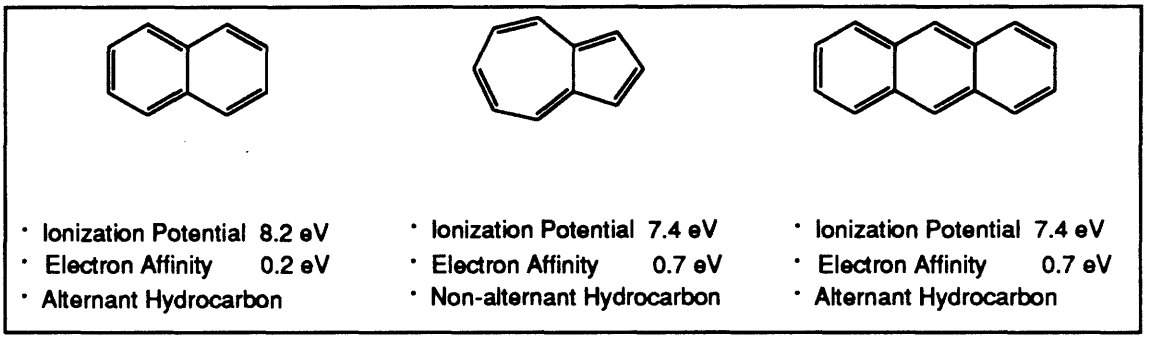
In 1976, Michl proposed a solution to the question of azulene's color based on simple molecular orbital theory.[8] In this paper, the ionization potential (a measure of the HOMO energy) and the electron affinity (a measure of the LUMO energy) for azulene and related compounds were considered (Scheme 1). When compared to naphthalene, the values indicated a smaller energy gap between the HOMO and LUMO for azulene. Since this energy gap is smaller, the wavelength of light necessary for this transition is longer and falls within the visible portion of the spectrum. Thus, azulene is blue, while naphthalene is colorless. However, the picture is complicated when the comparison is drawn between azulene and anthracene. Here the gap calculated on the basis of ionization potential (IP) and electron affinity (EA) is the same for both compounds, but anthracene is not blue!

The reason for this surprising result is that the difference in energy between the HOMO and LUMO cannot really be calculated based on ionization potential and electron affinity alone. Electron affinity refers to the energy involved in placing an electron in the LUMO of a molecule with a filled HOMO. In electronic excitation, however, an electron goes into the LUMO of a molecule which has only one electron in the HOMO. The

[8]Michl, J.; Thulstrup, E. W. *Tetrahedron* **1976**, *32*, 205.

difference between the actual HOMO-LUMO energy and that calculated based on IP and EA thus is affected by the repulsion between electrons in the HOMO and the LUMO. The degree of repulsion depends on the coefficients at each atom in these orbitals.

Scheme 1



What is different about azulene and anthracene is that azulene is a *non-alternant hydrocarbon* whereas anthracene, and for that matter naphthalene, is an *alternant hydrocarbon*. A characteristic of neutral alternant hydrocarbons is that their HOMO and LUMOs occupy the same region of space; this is not the case for non-alternant hydrocarbons. Thus, Michl states, "the reason why azulene is blue while anthracene is white, in spite of their similar ionization potentials and electron affinites, thus ultimately can be sought in the fact that the HOMO and LUMO of azulene are localized largely in different parts of space in the azulene molecule, and this is only possible because azulene is 'non-alternant' while they are localized in the same parts of space in the anthracene molecule, as they must be, since anthracene is alternant."

Naturally Occurring Azulenes

As has been previously mentioned, nature is a convenient source for a number of azulenes; guaiazulene is the most abundant. This compound, however, represents only a

small fraction of the azulenes that have been isolated from both plants and animals.[9] Several recent articles have increased the pool of naturally occurring azulenes (Table 1). In 1985, Dhar and co-workers reported the isolation of a C-formylated azulene derivative from the mushroom *Lactarius detterimus*.[10] This compound was structurally related to the previously known lactaroviolin (**1**)[11] and was found to be 11,12-dihydrolactaroviolin (**2**). Sterner and co-workers, in 1988, discovered that **1**, **2**, and the previously known lactarazulene (**3**)[12] were produced in other species of *Lacatarus* mushrooms.[13] Along with these derivatives, they unearthed another azulene, deterrol (**4**). These azulenes appear to serve as a defense mechanism for the mushroom, as the concentration of both **1** and **4** increase after injury to the fruit body.[17] Two of these compounds, lactaroviolin and deterrol, may have further use as pharmaceutical agents, as both have exhibited moderate cytotoxic activity against Ehrlich ascitic tumor cells and lymphocytic leukemia L-1210 cells, and deterrol showed mild antibiotic properties against *Acinetobacter calcoaceticus*.[14]

Several derivatives of 1,4-dimethylazulene have also recently been observed in a variety of plant sources. King reported the presence of three azulenes in the aerial parts of *Ixiolaena leptolepis*.[15] These included 1-carbomethoxy-4-methylazulene (**5**), 1,4-dicarbomethoxyazulene (**6**), and 1-carbomethoxyazulene-4-carboxaldehyde (**7**). Shortly after this report, King and Robinson found these same derivatives in the aerial parts of various *Helichrysum* species.[16]

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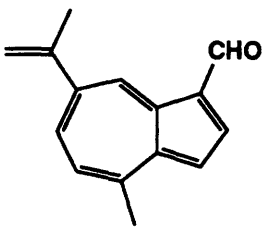
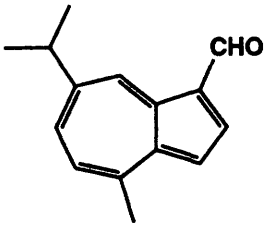
[9]Haagen-Smit, A. J. *Fortschr. Ch. Org. Naturst.* **1948**, *5*, 40.
[10]Koul, S. K.; Taneja, S. C.; Ibraham, S. P.; Dhar, K. L.; Atal, C. K. *Phytochemistry* **1985**, *24*, 181.
[11]Heilbronner, E.; Schimd, R. *Helv. Chim. Acta* **1954**, *37*, 2018.
[12]Sorm, F.; Benesova, V.; Herout, V. *Coll. Czech. Chem. Commun.* **1953**, *19*, 357.
[13]Bergendorff, O.; Sterner, O. *Phytochemistry* **1988**, *27*, 97.
[14]Anke, H.; Bergendorff, O.; Sterner, O. *Phytochemistry* **1989**, *27*, 393
[15]Lehmann, L.; Jakupovic, J.; Bohlmann, F.; King, R. M.; Haegi, L. *Phytochemistry* **1988**, *27*, 2994.
[16]Jakupovic, J.; Schuster, A.; Bohlmann, F.; Ganzer, U.; King, R. M.; Robinson, H. *Phytochemistry* **1989**, *28*, 543.

Table 1

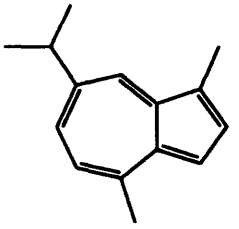
Azulenes from *Lacatarus* Mushrooms



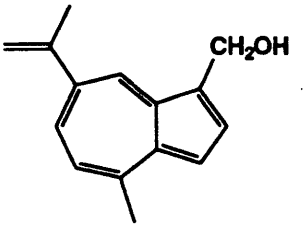
lactaroviolin
1



11,12-dihydrolactaroviolin
2

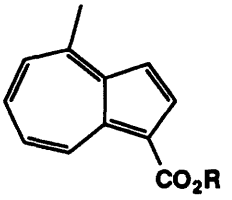


lactarazulene
3

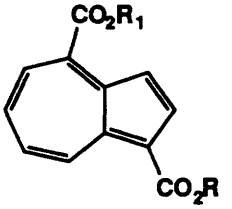


deterrol
4

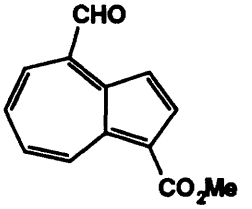
Naturally Occurring 1,4-Dimethylazulene Derivatives



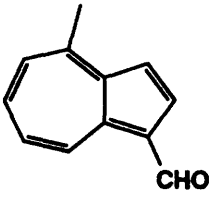
R = Me, **5**
R = H, **9**



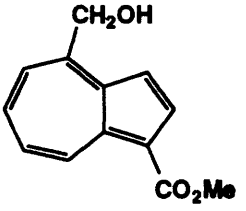
R_1 = Me, R = Me, **6**
R_1 = H, R = Me, **10**
R_1 = H, R = H, **11**



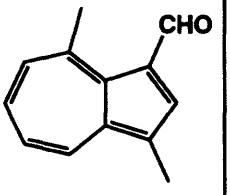
7



8



12

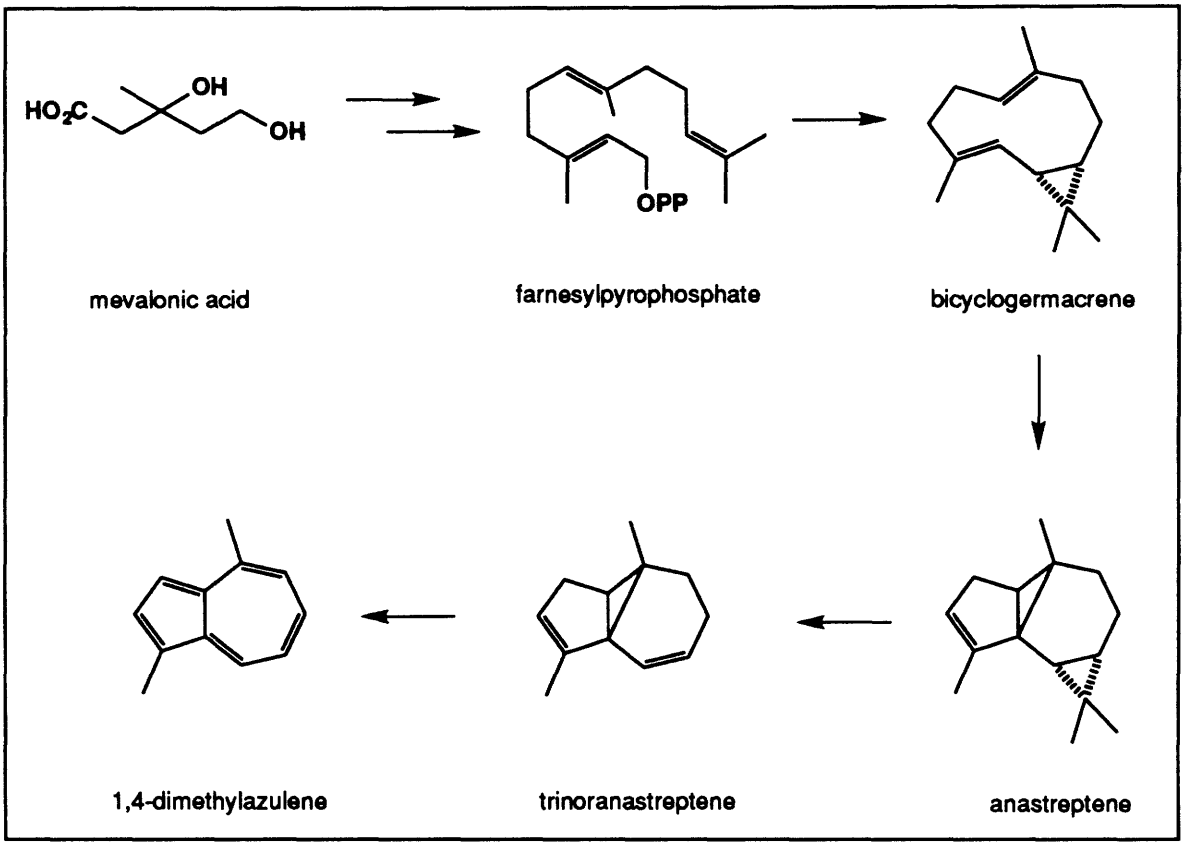


13

The liverworts have also proved to be a rich source of azulenes. Katoh and co-workers isolated two new 1,4-dimethylazulene derivatives from *Calypogeia azurea*, 4-methylazulene-1-carboxaldehyde (**8**) and 4-methylazulene-1-carboxylic acid (**9**), as well as

5 and 1,4-dimethylazulene.[17] A separate investigation of this liverwort by Siegel provided more azulene derivatives, including **10-13**, as well as **7** and **9**.[18] This paper also provided information on azulenes from another liverwort, *Plagiochila longispina.* All of these 1,4-dimethylazulene derivatives presumably are formed in a similar manner in most liverworts. Katoh has proposed the following biosynthetic pathway for the production of these compounds (Scheme 2).[18]

Scheme 2



[17]Nakagawara, S.; Katoh, K.; Kusumi, T.; Komura, H.; Nomoto, K.; Konno, H.; Huneck, S.; Takeda, R. *Phytochemistry* **1992**, *31*, 1667.
[18]Siegel, U.; Mues, R.; Dönig, R.; Eicher, Th.; Blechschmidt, M.; Becker, H. *Phytochemistry* **1992**, *31*, 1671.

Commerical Applications of Azulenes

Azulenes are incorporated in a wide array of commercially interesting applications in such fields as cosmetics and pharmaceuticals. A recent survey of the patent literature revealed that a number of azulenesulfonic acid derivatives and their salts were active components in hair treatment preparations.[19] The use of these compounds in other areas such as dental products has also been reported. Sodium 3-guaiazulene sulfonate (**14**) has been demonstrated to be effective in the treatment of a variety of periodontal diseases.[20]

The Kotobuki Seiyaku company has been an active leader in the development of pharmaceuticals incorporating azulene derivatives. Their most successful compound to date is the anti-ulcerative *Azuletil sodium* (KT1-32, **15**).[21] A detailed review of this drug and other similar ulcer medications will be presented in a later chapter. Along with KT1-32, researchers at Kotobuki have also recently developed a new class of non-prostanoid thromboxane A_2 (TXA_2) receptor antagonists incorporating an azulene sulfonate.[22] Among the derivatives prepared, one compound, KT2-962 (**16**), possessed potent TXA_2 inhibitory properties at a concentration of 9.0×10^{-10} M.[23] This derivative also proved to be a selective inhibitor of vascular contraction and had no TXA_2 synthetase inhibitory effect at this concentration.[22] Furthermore, KT2-962 has been examined for possible use in the prevention and treatment of acute renal failure,[24] and when co-administered with

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[19]Itou, T.; Kajino, T.; Miyaji, A.; Yoshihara, T.; Kawase, J.; Matubara, M.; Kure, N. *Eur. Pat. Appl. EP 529,437 CA* **1993**, *118*:219458u.

[20]Danjo, K.; Ootsuka, A.; Wakimoto, T. *Jpn. Kokai Tokkyo Koho JP 04 59,723 [92 59,723] CA* **1992**, *117*:33730a.

[21]Yanagisawa, T.; Wakabayashi, S.; Tomiyama, T.; Yasunami, M.; Takase, K. *Chem. Pharm. Bull.* **1988**, *36*, 641.

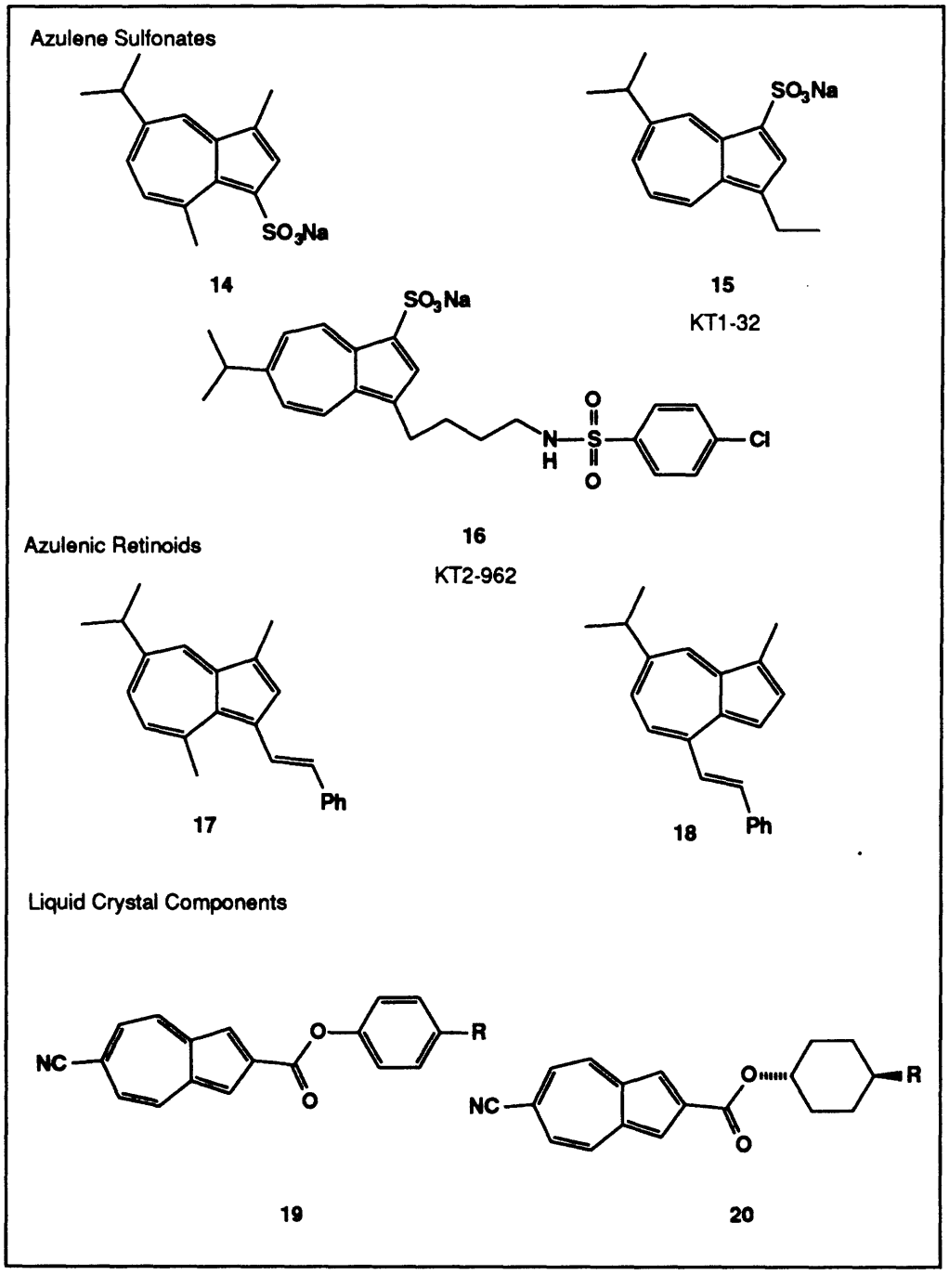
[22]Tomiyama, T.; Wakabayashi, S.; Kosakai, K.; Yokota, M. *J. Med. Chem.* **1990**, *33*, 2326.

[23]Tomiyama, T.; Yokota, M.; Wakabayashi, S.; Kosakai, K.; Yanagisawa, T. *J. Med. Chem.* **1993**, *36*, 791.

[24](a) Chun, S. H.; Kang, J. S.; Suh, T. K. *Hanyang Uidae Haksulchi* **1992**, *12*, 119; *CA* **1992**, *117*:84088e. (b) Ko, H. C.; Kang, S. J.; Suh, T. K. *Hanyang Uidae Haksulchi* **1992**, *12*, 395; *CA* **1992**, *117*:83146k.

cyclosporin A (CsA), this compound has been demonstrated the ability to suppress CsA-induced nephrotoxicity in rats.[25]

Table 2



[25]Kim, K. S.; Kang, J. S.; Suh, T. K. *Hangyang Uidae Haksulchi* **1992**, *12*, 541; *CA* **1993**, *118*:52056x

A number of other azulene derivatives are currently being examined as possible pharmaceutical agents. Researchers at Parke-Davis have recently reported the synthesis and biological activity of several azulenic retinoids.[26] Two analogs **17** and **18**, both derived from guaiazulene, possessed moderate inhibitory properties against carcinogen-induced neoplastically transformed foci.[27] Further studies of these interesting nonbenzenoid retinoids are currently being conducted.

The utility of azulenes is not limited to the field of pharmaceuticals. As is easily imagined, these highly colored compounds are useful as dyes, particularly in laser printing applications and xerography.[1g] Recently, the Mitsubishi Kasei Corporation has been active in creating liquid crystal displays incorporating a variety of azulenes.[28] A number of patents for various cyanoazulene derivatives such as **19** and **20** have recently been issued claiming excellent display characteristics for LCDs employing these compounds.[29]

From this brief review, it is fairly obvious that the exploitation of azulenes and their unique properties is in its infancy. While the potential for many exciting and useful applications for these compounds is high, prospects for rapid growth of the field is limited by the current technology available for the creation of "designer azulenes."

Classical Azulene Syntheses

The ability to create specific synthetic azulenes has been sought after for more than 50 years. During this period, two distinct approaches have been developed. Classical

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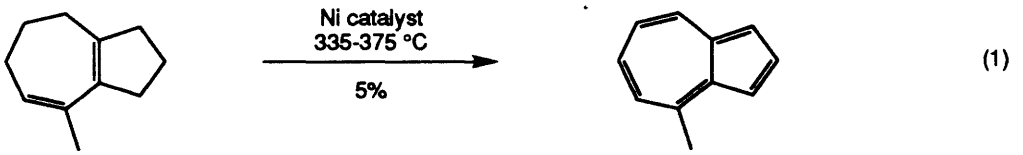
[26](a) Asato, A. E.; Li, X. -Y.; Mead, D.; Patterson, G. M. L.; Liu, R. S. H. *J. Am. Chem. Soc.* **1990**, *112*, 7398. (b) Liu, R. S. H.; Liu, C. W.; Li, X. -Y.; Asato, A. E. *Photochem. Photobiol.* **1991**, *54*, 625.

[27]Asato, A. E.; Peng, A.; Hossain, M. Z.; Mirzadegan, T.; Bertram, J. S. *J. Med. Chem.* **1993**, *36*, 3137.

[28]Morita, T.; Kaneko, M. *Jpn. Kokai Tokkyo Koho JP 03,122,189 [91,122,189] CA* **1992**, *116*:117404q.

[29]Morita, T.; Kaneko, M. *Jpn. Kokai Tokkyo Koho JP 03,261,754 [91,261,754] CA* **1992**, *116*:117465k, 117466m.

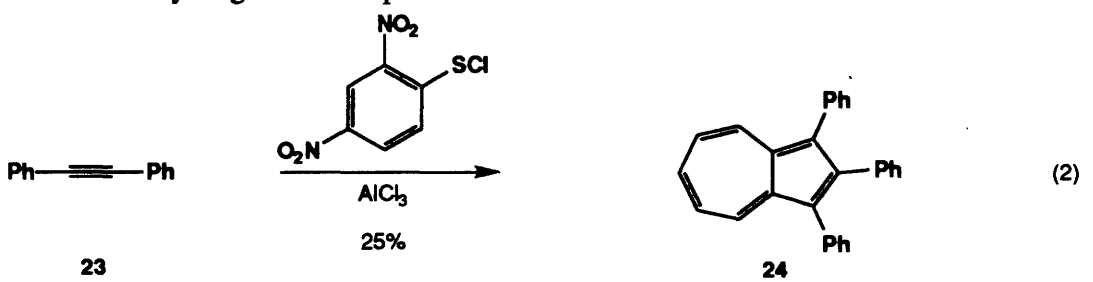
methods for the synthesis of azulenes have relied heavily on a dehydrogenative approach in which a suitable *hydroazulene* precursor is oxidized to the fully aromatic product. In fact, the landmark 1936 synthesis of 4-methylazulene (**22**) by Pfau and Plattner used this strategy (eq 1).[7] It is evident, however, that this type of an approach is severely limited in scope. Since the key dehydrogenation step requires very harsh reaction conditions, this method all but forbids the inclusion of sensitive functionality in the hydroazulene precursor. Furthermore, low yields are generally the rule for this process. By altering the catalyst and reaction conditons, advances in the dehydrogenative approach have been realized; however, yields are only marginally improved,[30] and this method is still far less attractive than routes which eliminate the need for a separate dehydrogenation step.



(1)

21 **22**

In 1954, the first method of forming azulenes without a separate dehydrogenation step was reported by Kharasch.[31] The dimerization of diphenylacetylene (**23**) in the presence of 2,4-dinitrobenzenesulfenyl chloride and aluminum trichloride resulted in the formation of 1,2,3-triphenylazulene (**24**) in low yields (eq 2). Subsequently, Ziegler and Hafner developed what is probably the best known procedure for azulene synthesis which obviates the dehydrogenation step.[32]



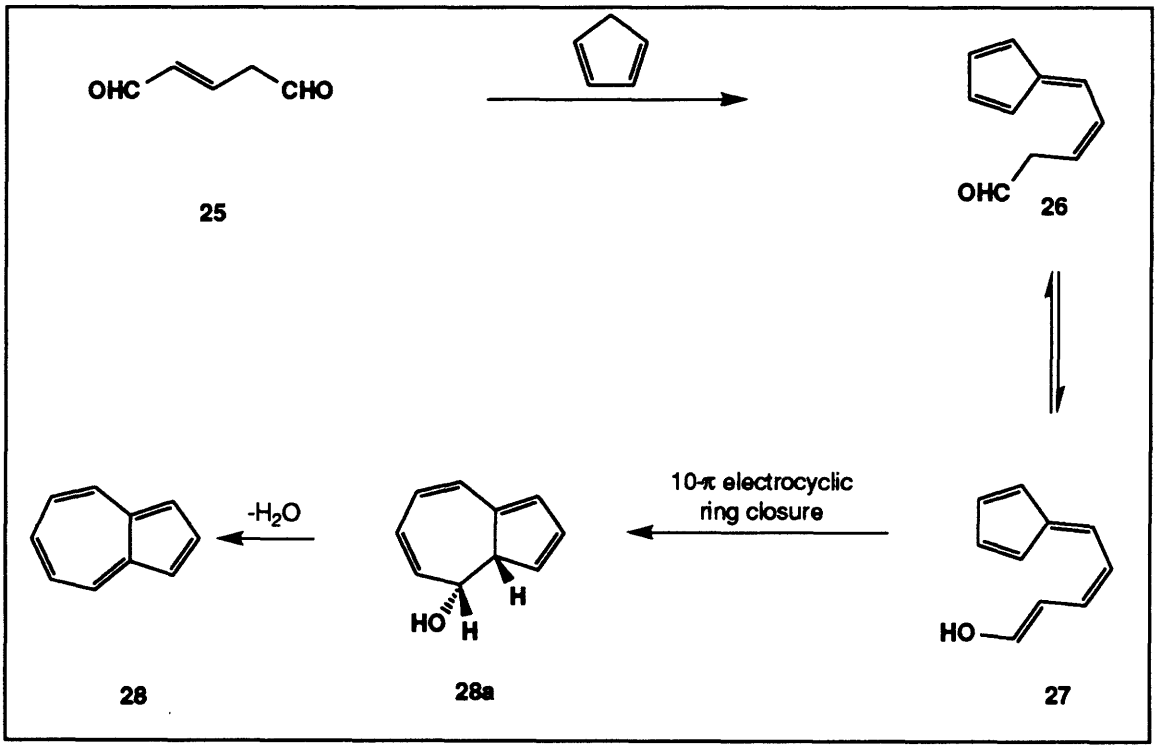
(2)

23 **24**

[30]Kovats, E.; Günthard, Hs. H.; Plattner, Pl. A. *Helv. Chim. Acta* **1954**, *37*, 2123.
[31]Assony, S. J.; Kharasch, N. *Chem. Ind.* **1954**, 1388.
[32] (a) Ziegler, K.; Hafner, K. *Angew. Chem.* **1955**, *67*, 301. (b) Hafner, K. *Angew. Chem.* **1955**, *67*, 301.

This reaction involves the condensation of glutacondialdehyde with cyclopentadiene. The resulting fulvene intermediate **26** then undergoes a thermally-induced 10-π electrocyclic ring closure, followed by dehydration to form azulene (Scheme 3). The instability of glutacondialdehyde (**25**) precludes using it directly; various pyridinium salts, however, can function as glutacondialdehyde equivalents, making the Ziegler-Hafner process a reliable method for azulene synthesis.[33]

Scheme 3

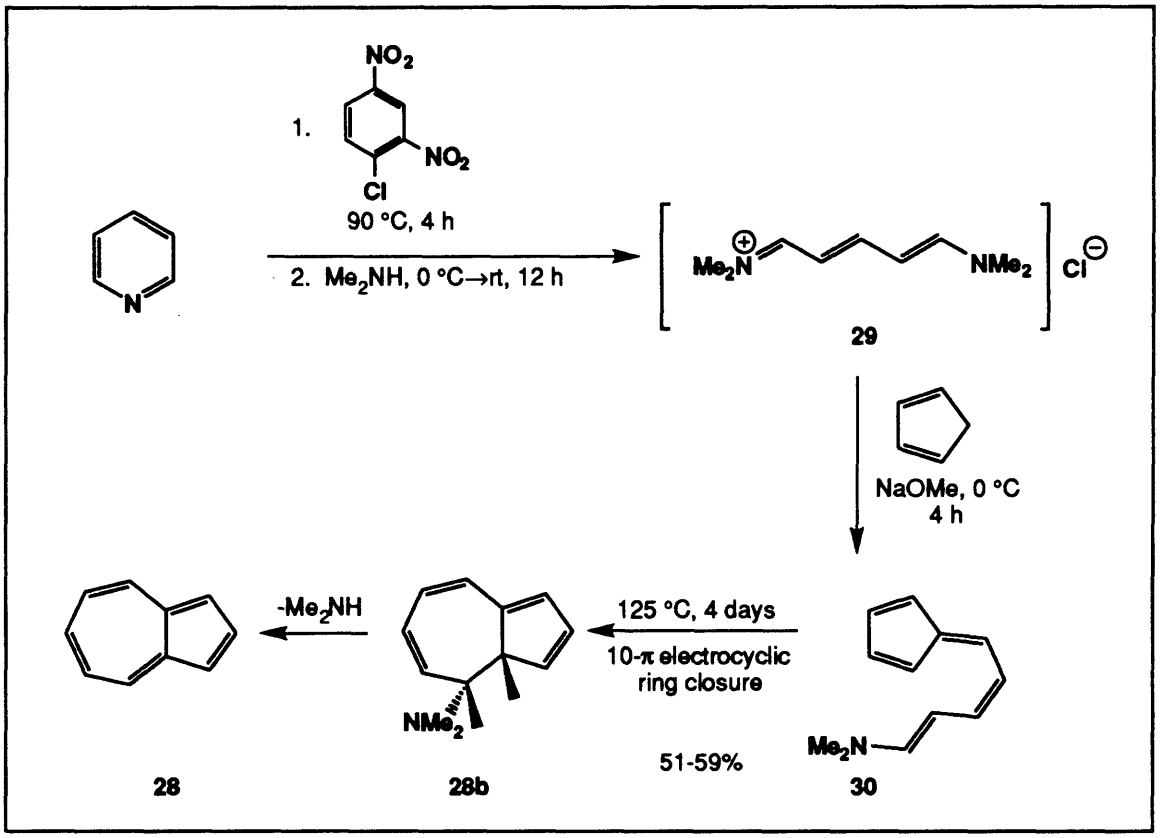


The parent azulene hydrocarbon has recently been the subject of an *Organic Syntheses* preparation.[34] The process involves the *in situ* generation of **29** followed by

[33] For some representative examples of the Ziegler-Hafner approach see: (a) Hafner, K. *Liebigs Ann. Chem.* **1957**, *606*, 79. (b) Hafner, K.; Asmus, K. -D. *Liebigs Ann. Chem.* **1964**, *671*, 31. (c) Porshnev, Y. N.; Tereshchenko, E. M.; Churkina, V. A. *J. Org. Chem. USSR* **1974**, *10*, 887. (d) Hafelinger, G.; Ott, G. *Liebigs Ann. Chem.* **1984**, 1605.
[34] Hafner, K.; Meinhardt, K. -P. *Org. Synth. Coll. Vol. 7* **1990**, 15.

condensation with sodium cyclopentadienide to give the fulvene intermediate **30**. Thermal cyclization of **30** in refluxing pyridine effects the 10-π electrocyclic ring closure and elimination of dimethylamine (Scheme 4). A laborious isolation procedure involving a time-consuming Soxhlet extraction, problematic acid washes to remove residual pyridine, and chromatography on neutral alumina provides azulene (**28**) as blue plates in 51-59% yield.[35] Perhaps the current commercial price of $90 for one gram of azulene is a good reflection of these difficulties.

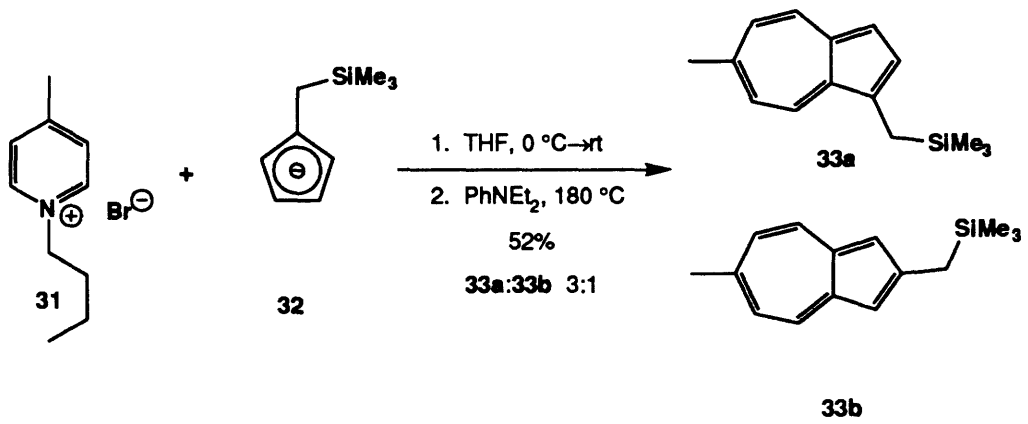
Scheme 4



Substituted azulenes can also be produced by the Ziegler-Hafner method. Here, the reaction of N-alkylpyridinium salts with sodium cyclopentadienides can result in the

[35]The scale of the reaction appears to have an effect on the yield of azulene obtained by this process, presumably due to mechanical losses. For instance, on a 0.1 mol scale, the overall yield is 39%, while on a 0.8 mol scale, the yield soars to 79%. See ref. 34.

formation of azulenes substituted on either the five or seven-membered ring.[36] Substituted pyrylium salts also undergo this reaction, and these cases offer the advantage of a much lower reaction temperature (-20 °C versus 200 °C for the pyridinium salts) but unfortunately, this reaction fails for the unsubstituted pyrylium tetrafluoroborate. When the cyclopentadienide component is substituted, regioisomeric products can be formed (eq 3). For example, the reaction of lithium 1-(trimethylsilylmethyl)cyclopentadienide (**31**) with pyridinium salt **32** results in an inseparable mixture of the two azulene products **33a** and **33b**.[37]



(3)

This regiochemical problem is compounded by the difficulties encountered in the synthesis of highly substituted cyclopentadienides and the sometimes tedious isolation techniques (not to mention high reaction temperatures) necessary to obtain the azulene products from the reaction mixture. All of these factors conspire to limit the utility of the Ziegler-Hafner process. This procedure, however, is still the best choice for the synthesis of the parent azulene itself, and it should be recognized as an important method for the creation of substituted derivatives.

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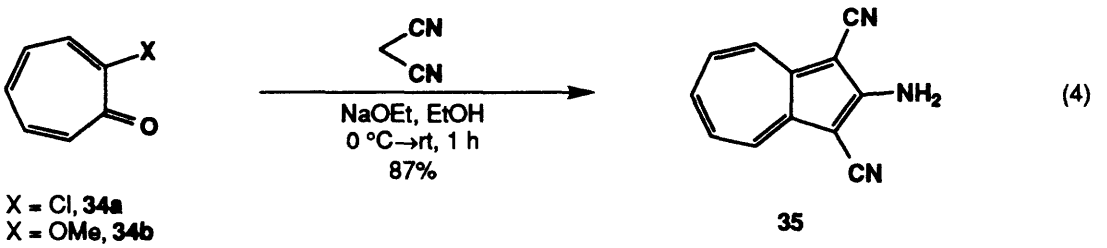
[36]Hafner, K.; Kaiser, H. *Liebigs Ann. Chem.* **1958**, *618*, 140.
[37]Rudolf, K.; Robinette, D.; Koenig, T. *J. Org. Chem.* **1987**, *52*, 641.

Azulenes from Troponoids

While the preceding work was being carried out in Germany, researchers in Japan began to examine a new route to 1,2,3-trisubstituted azulenes based on tropone derivatives.[38] Nozoe and co-workers demonstrated that 2-chloro or 2-methoxytropone (**34a,b**) reacts with ethyl cyanoacetate or malononitrile in the presence of excess sodium ethoxide in ethanol to form azulenic products (eq 4).[39] Several years later, Seto determined that these tropone derivatives react with various malonate derivatives (eq 5) to produce 2H-cyclohepta[b]furan-2-ones or 2H-cyclohepta[b]furan-2-imines.[40] Subsequent reexamination by Nozoe and Takase indicated that these lactones were intermediates in their previously reported reactions. Furthermore, they determined that by treating these cyclohepta[b]furan-2-ones with malonates in the presence of excess sodium ethoxide in ethanol, 2-hydroxy or 2-aminoazulenes were produced (eq 6).[41] As illustrated in eq 7, reaction of 2-(*p*-tolylsulfonyloxy)tropone (**38**) with malonates does not occur by displacement of the leaving group, as is seen for 2-chlorotropone. Rather, 1,8-addition of the nucleophile followed by base-induced elimination of an arylsulfinate ion gives rise to hydroxy lactone **39**. Further reaction of **39** with malonates provides 8-hydroxyazulenes.[42]

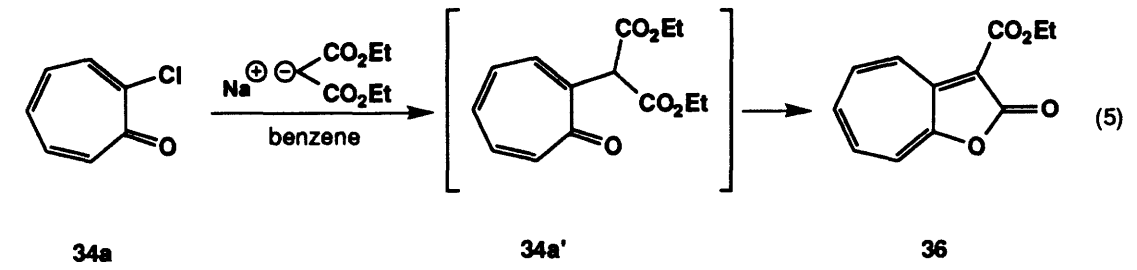


X = Cl, **34a**
X = OMe, **34b**

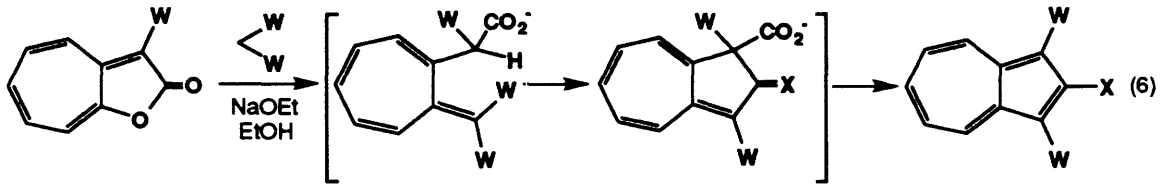
35

(4)

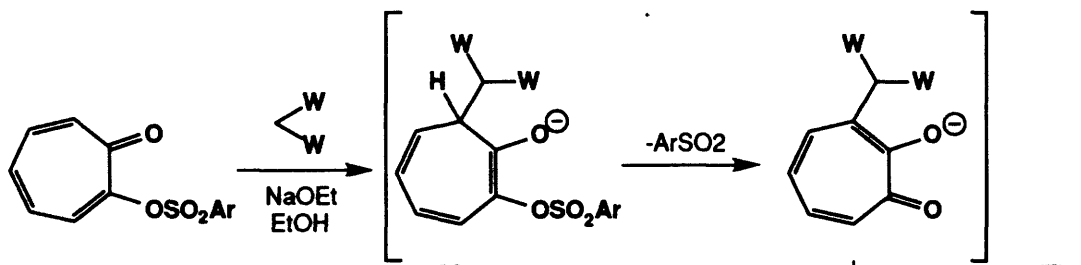
[38]Nozoe, T.; Matsumura, S.; Murase, Y.; Seto, S. *Chem. Ind.* **1955**, 1257.
[39]Nozoe, T.; Seto, S.; Matsumura, S.; Murase, Y. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 1179.
[40]Seto, S. *Sci. Repts. Tohoku Univ.* **1953**, *37*, 367.
[41]Nozoe, T.; Takase, K.; Shimazaki, N. *Bull. Chem. Soc. Jpn.* **1962**, *37*, 1644.
[42]Nozoe, T.; Takase, K.; Kato, M.; Nogi, T. *Tetrahedron* **1971**, *27*, 6023.



34a 34a' 36

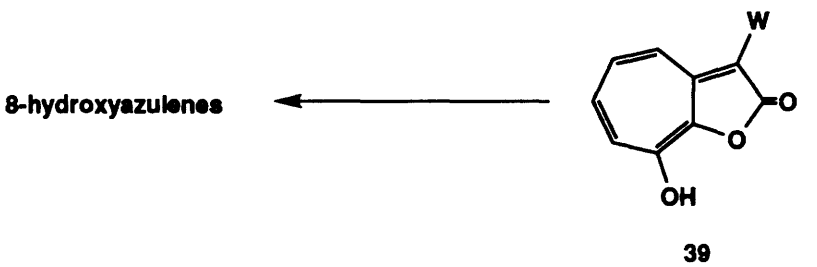


36 W = CO_2R, CN 36a 36b X = OH, **37a** X = NH_2, **37b**



38 38a 38b

W = CO_2R, CN



39

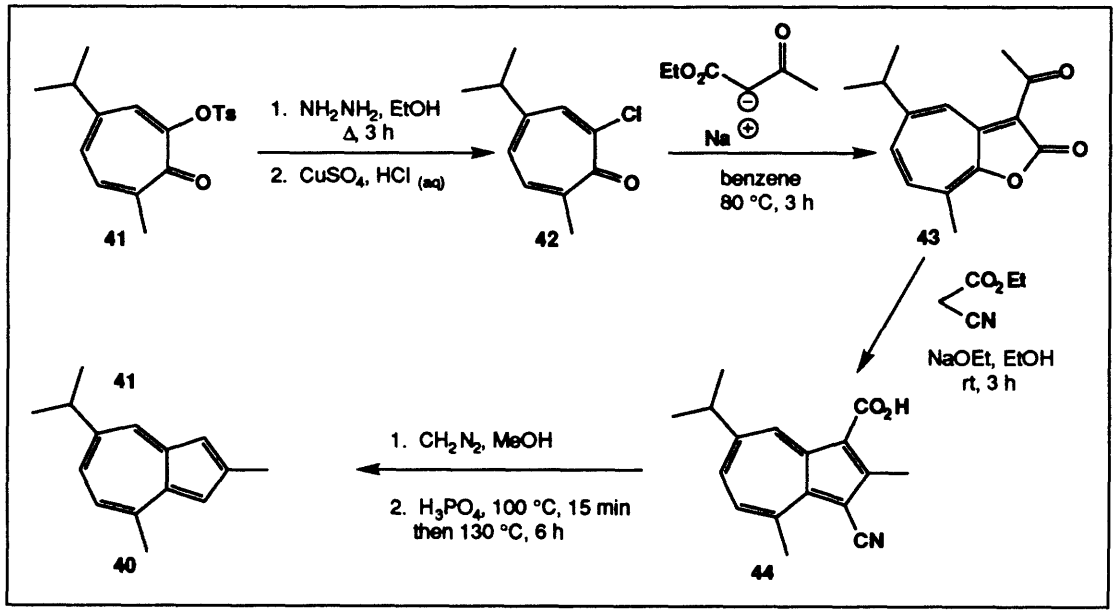
Nozoe and Takase were also able to apply this new process to create azulenes substituted on the seven-membered ring as illustrated in their report of the synthesis of Se-guaiazulene (**40**) (Scheme 5).[43] Nucleophilic displacement of the tosylate of 4-isopropyl-7-methyl-2-(p-tolylsulfonyloxy)tropone[44] (**41**) with ethanolic hydrazine, followed by

[43]Nozoe, T.; Takase, K.; Fukuda, S. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 2215.

[44]This material is available in 6 steps from 4-isopropylcyclohexane. See: (a) Cook, J. W.; Raphael, R. A.; Scott, A. I. *J. Chem. Soc.* **1951**, 695. (b) Kitahara, Y.; Kato, T. *Bull. Chem. Soc., Jpn.* **1964**, *37*, 859.

oxidative decomposition of the resulting hydrazinotropone intermediate with $CuSO_4$ and HCl resulted in the formation of the 2-chlorotropone derivative **42**. This material was then treated with ethyl sodioacetoacetate in benzene to form the furanone **43**, which in turn provided azulene **44** after exposure to ethyl sodiocyanoacetate in ethanol. Removal of the acid and nitrile moieties by decarboxylation provided Se-guaiazulene.

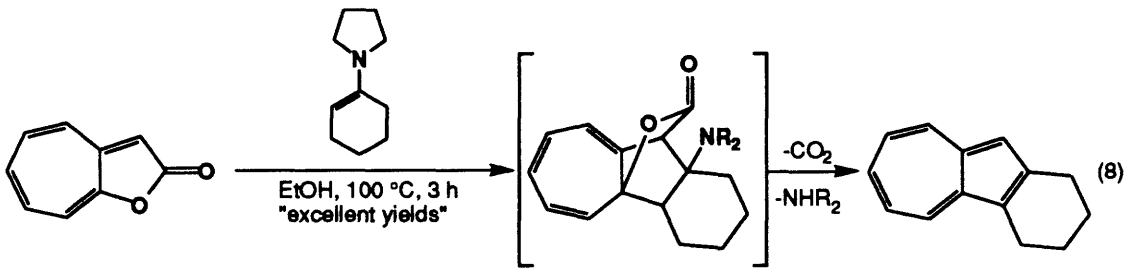
Scheme 5



In 1971, Nozoe and Takase demonstrated that these bicyclic lactones generated from the addition of active methylenes to substituted tropones participate in an [8+2] cycloaddition with cyclic enamines to give 1,2-disubstituted polycyclic azulenes.[45] Eq 8 shows a typical example of this interesting azulene synthesis. This report was followed by several voluminous papers which detail [8+2] reactions with other 2-carbon components

[45]Yang, P. -W.; Yasunami, M.; Takase, K. *Tetrahedron Lett.* **1971**, 4275.

such as enamines of acyclic aldehydes and ketones,[46] vinyl ethers,[47] acetals,[48] orthoesters,[49] and furan derivatives.[50] This method can also be used to create azulenes substituted on the seven-membered ring by starting from substituted furanones.



45 45a 46

The methods described above allow for the construction of azulenes not generally available via other methods. In particular, the ability to install heteroatoms at C-2 and C-8 is unique to these methods. Another attractive feature is the incorporation of functionality (CN or CO_2R) at C-3 which can be easily removed from the azulene. Regiochemical control over the products is generally very good, except in the cases where enamines of acyclic ketones and unsymmetrical acetals are employed. For example, the reaction of furanone **47** with the dimethyl acetal of ethyl methyl ketone gives a 3:1 mixture of **48a** and **48b**, due to the formation of two isomeric intermediate vinyl ethers under the reaction conditions (eq 9). The major drawback to this approach is the availability of the requisite cyclohepta[b]furan-2-ones; these compounds are not commercially available and must be prepared from the corresponding tropone derivatives. Furthermore, substituted tropones must also be synthesized via multistep processes.

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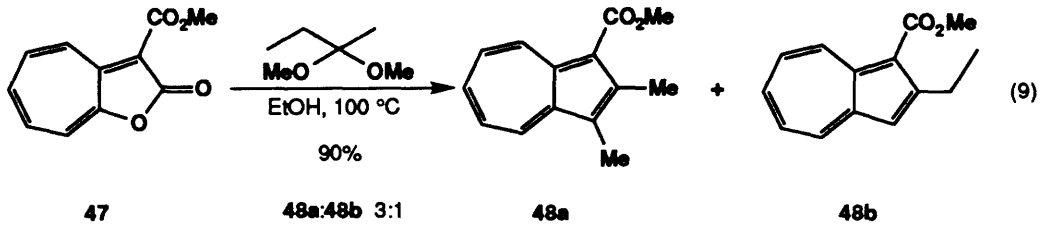
[46]Yasunami, M.; Chen, A.; Yang, P. -W.; Takase, K. *Chem. Lett.* **1980**, 579.
[47]Nozoe, T.; Yang, P. -W.; Wu, C. -P.; Huang, T. -S.; Lee, T. -H.; Okai, H.; Wakabayashi, H.; Ishikawa, S. *Heterocycles* **1989**, *29*, 1225.
[48]Nozoe, T.; Wakabayashi, H.; Ishikawa, S.; Wu, C. -P.; Yang, P. -W. *Heterocycles* **1990**, *31*, 17.
[49]Nozoe, T.; Wakabayashi, H.; Shindo, K.; Ishikawa, S.; Wu, C. -P.; Yang, P. -W. *Heterocycles* **1991**, *32*, 213.
[50]Wakabayashi, H.; Yang, P. -W.; Wu, C. -P.; Shindo, K.; Ishikawa, S.; Nozoe, T. *Heterocycles* **1992**, *34*, 429.



Azulenes from Tropylium Ions

In 1989, Becker and Danheiser reported a new [3+2] approached to 2-silylazulenes based on the reaction of 2 equivalents of tropylium tetrafluoroborate with various allenylsilanes.[51] As outlined below in Scheme 6, $TpBF_4$ (**49**) reacts with 1,3-dialkyl(*t*-butyldimethylsilyl)allenes to generate the stabilized β-silicon carbocation **51**. 1,2-Silyl group migration followed by cyclization to cycloheptadienyl cation **53** and elimination of a proton gives dihydroazulene **54**. The second equivalent of $TpBF_4$ abstracts hydride from **54** to afford the azulenium cation **55**, which by deprotonation provides the product azulenes. In order to realize synthetically useful yields of the products, a non-nucleophilic acid scavenger was employed to remove HBF_4; poly(4-vinylpyridine) and methyltrimethoxysilane proved to be effective in this capacity.

This method is useful for constructing 1,2,3-trisubstituted azulenes in a regioselective manner (eq 10). The 2-silyl group can be removed easily by protodesilylation to provide access to 1,3-dialkylazulenes. Reactions involving allenylsilanes without a C-1 substituent fail because in these cases an unfavorable rearrangement of a secondary to primary vinyl cation is required. Allenylsilanes lacking a C-3 substituent give lower yields of the expected 1,2-disubstituted azulene due to electrophilic substitution at C-3 in the newly formed azulene by excess $TpBF_4$.

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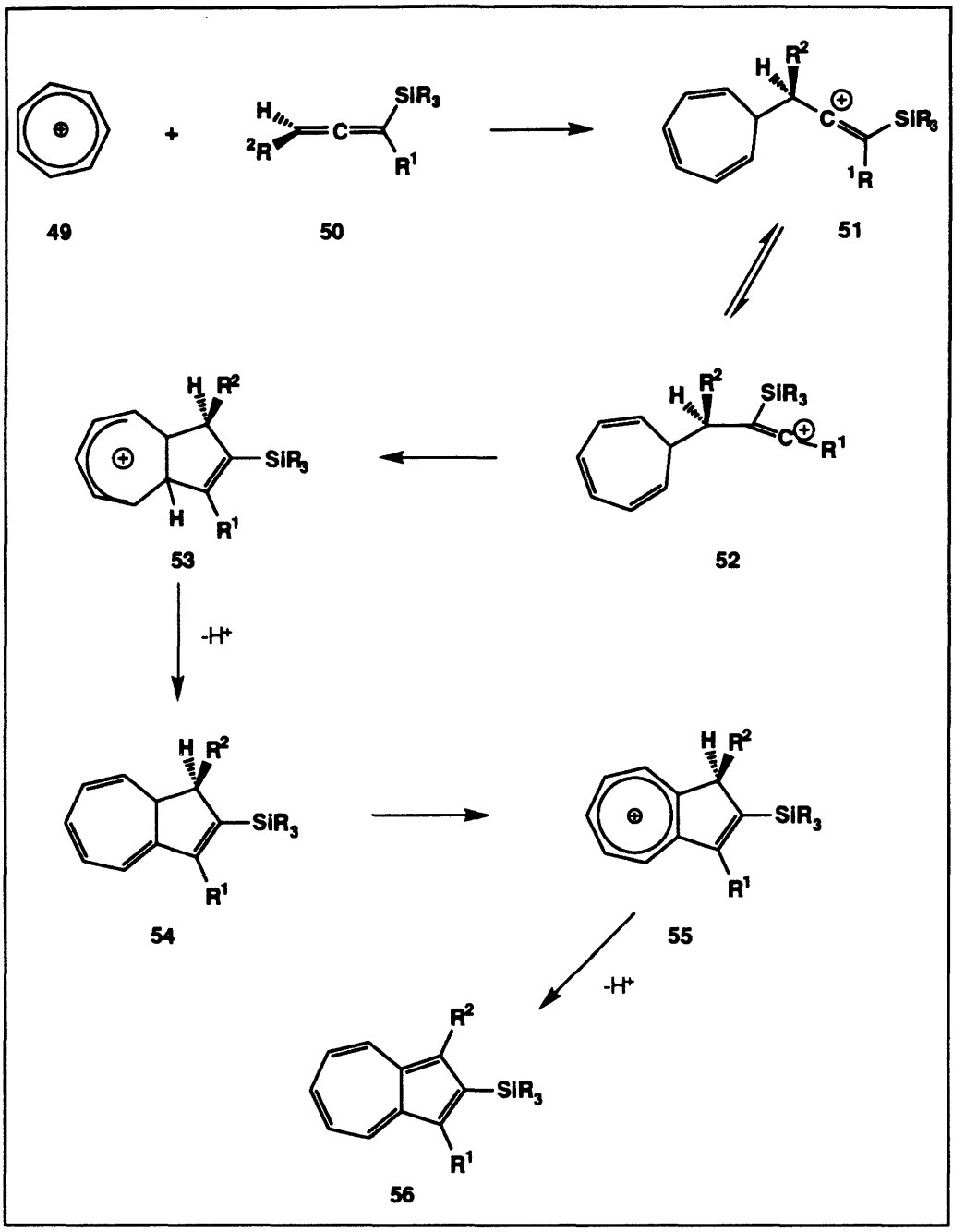
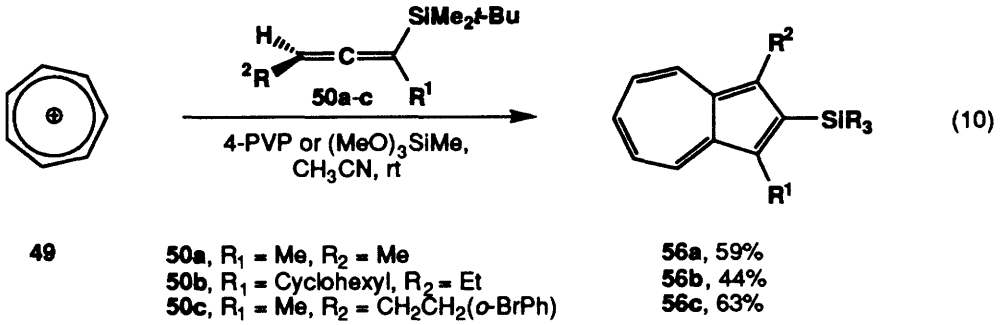
[51]Becker, D. A.; Danheiser, R. L. *J. Am. Chem. Soc.* **1989**, *111*, 389.

Scheme 6



This approach is also of limited utility for creating azulenes substituted on the seven-membered ring. Substituents on the tropylium ring are limited to those that bear no α-hydrogens. Thus, reaction of phenyl and *t*-butyltropylium tetrafluoroborate with

allenylsilanes does give rise to azulenic products; however, a mixture of regioisomers is formed with the 5-substituted product predominating in both cases (eq 11).

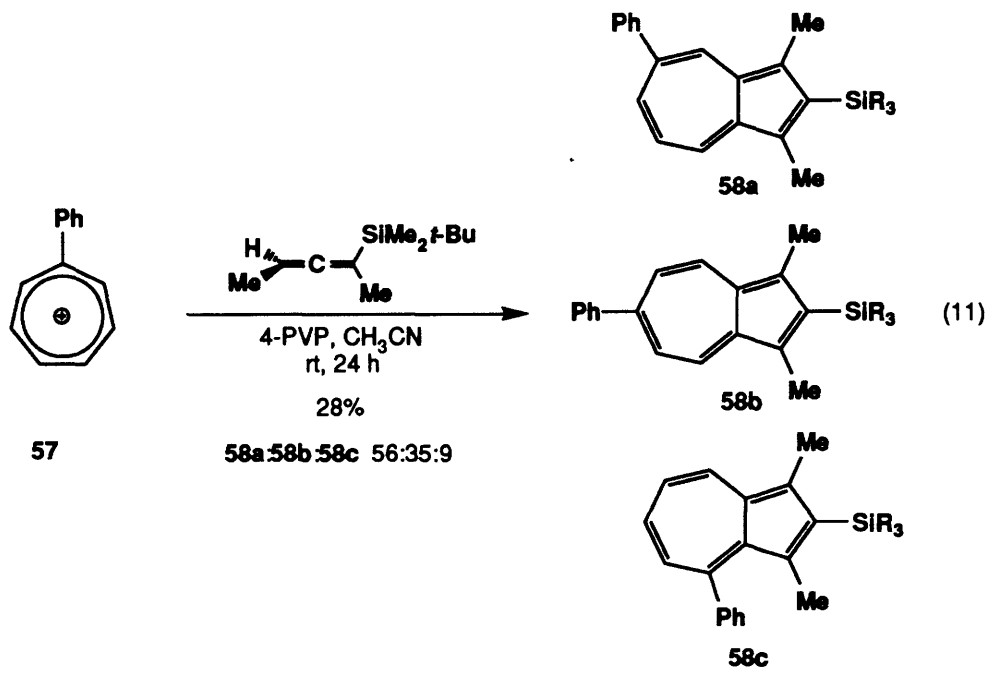


(10)

49

50a, R_1 = Me, R_2 = Me
50b, R_1 = Cyclohexyl, R_2 = Et
50c, R_1 = Me, R_2 = CH_2CH_2(*o*-BrPh)

56a, 59%
56b, 44%
56c, 63%



(11)

57

58a:**58b**:**58c** 56:35:9

Several observations can be made concerning the current status of the art of azulene synthesis. The production of azulenes substituted on the five-memberd ring can be accomplished under a variety of conditions with good to excellent regiochemical control and chemical yield. The same, however, cannot be said for azulenes bearing substituents on the seven-membered ring. The nature of substituents that can be incorporated into the products is also limited in many cases. The methods of Plattner, Ziegler, and to a certain

extent Nozoe and Takase employ harsh reaction conditions which make including sensitive functionality difficult. In real terms, the scope is limited to various polyalkylazulenes. A final concern is the availabilty of starting materials; here again, the reliance on materials that are expensive or that require multiple steps to produce restricts the possible utility of these methods. It is clear that there exists a need for new methods which can provide access to azulenes incorporating a wider range of substituents and functional groups, on both the five- and seven-membered rings.

New Approaches to the Synthesis of Substituted Azulenes

Several years ago, we became interested in developing a general azulene synthesis that would allow access to derivatives substituted on both the five and seven-membered rings. Our efforts to date have a common underlying theme; we have elected to focus our studies on *ring expansion-annulation strategies*. These approaches begin with substituted benzene derivatives as starting materials and employ an intramolecular carbenoid cycloaddition to expand the benzene ring to seven carbons while simultaneously generating the five-membered ring. An attractive feature of this approach is that it takes advantage of the ready availability of a large variety of substituted benzene derivatives which are commercially available or easy to prepare. Thus the ring expansion-annulation strategy is particularly well suited for the preparation of azulenes that bear substituents at specific positions on the seven-membered ring.

The ability to create cycloheptatrienes from benzenes via the Büchner reaction has been known since the late nineteenth century.[52] This process involves the addition of a carbene or carbenoid (generated thermally, photochemically, or by reaction with a metal catalyst) to aromatic systems to give a norcaradiene intermediate **60** followed by 6-π

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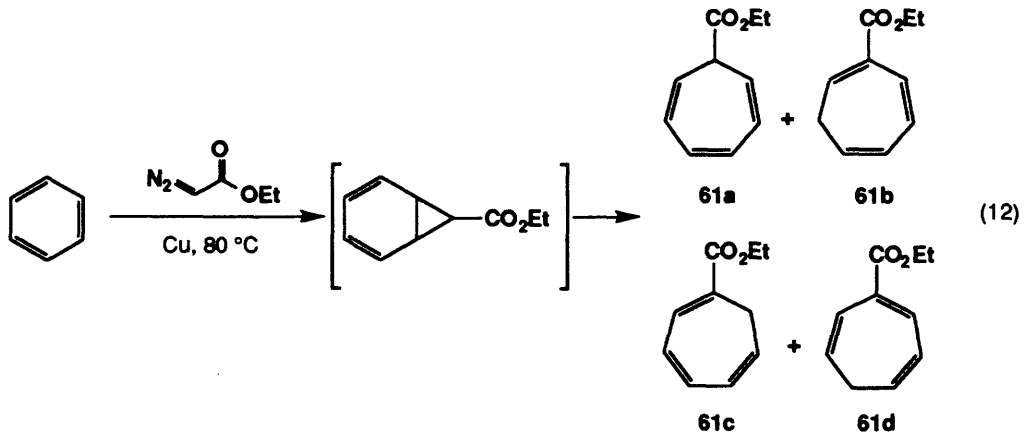
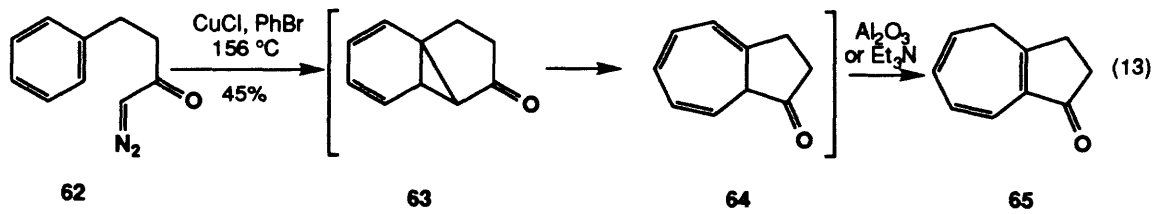
[52](a) Buchner, E.; Curtius, T. *Chem. Ber.* **1885**, *18*, 2371. Reviewed in (b) Dave, B.; Warnoff, E. W. *Org. Reactions* **1970**, *18*, 217. (c) Mass, G. *Top. Curr. Chem.* **1987**, *137*, 75. See also: (d) Burke, S. D.; Grieco, P. A. *Org. Reactions* **1979**, *26*, 361.

electrocyclic ring opening to give a mixture of cycloheptatrienes **61a-d** (eq 12). The intramolecular variant of this reaction has also been reported. Julia[53] and Scott[54] were the first to use this method to synthesize hydroazulenones, as shown in eq 13. By utilizing copper or its salts to generate the carbenoid species, these researchers were able to realize moderate yields of the desired bicyclic ketone. Dramatic increases in the efficiency of this process, however, were observed by modifying these reaction conditions.

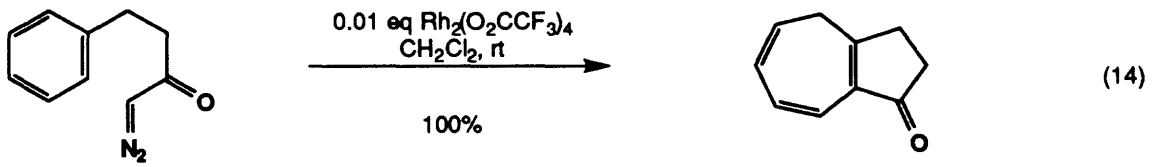




In 1976, Noels and Hubert reported that rhodium(II) carboxylates are extremely efficient catalysts for a variety of reactions of carbenoids derived from α-diazo carbonyl compounds.[55] In fact, by utilizing rhodium(II) trifluoroacetate as catalyst in the

[53]Costantino, A.; Linstrumelle, G.; Julia, S. *Bull. Chem. Soc. Fr.* **1970**, 907, 912.
[54](a) Scott, L. T. *J. Chem. Soc., Chem. Commun.* **1973**, 882. (b) Scott, L. T.; Minton, M. A.; Kirms, M. A. *J. Am. Chem. Soc.* **1980**, *110*, 6311.
[55](a) Hubert, A. J.; Noels, A. F.; Anciaux, A. J.; Teyssie, P. *Synthesis* **1976**, 600. (b) Anciaux, A. J.; Hubert, A. J.; Noels, A. F.; Petiniot, N.; Teyssie, P. *J. Org. Chem.* **1980**, *45*, 695. (c) Anciaux, A. J.; Demonceau, A.; Noels, A. F.; Hubert, A. J.; Warin, R.; Teyssie, P. *J. Org. Chem.* **1981**, *46*, 873. See

intermolecular Büchner reaction, only one regioisomer (**61a**) is formed, as opposed to the mixture generally obtained under the classical conditions (presumably due to a dramatically lower reaction temperatures possible in the rhodium-catalyzed process).[55b] In 1984, McKervey and coworkers applied this new catalyst to the intramolecular Büchner reaction and determined that the reaction proceeded in near quantitative yield at room temperature in dichloromethane (eq 14).[56] This group has also explored the scope and regiochemistry[56,57] of this process, and also has demonstrated its value for the total synthesis of various hydroazulene natural products.[58] Scott has recently developed this intramolecular Büchner reaction into an *Organic Syntheses* preparation using rhodium(II) acetate as the catalyst.[59]



62 65 (14)

While the intramolecular Büchner reaction is an excellent method for the synthesis of hydroazulenones, it is not a practical choice for producing azulenes. Scott has used this method to make the parent azulene hydrocarbon by heating the ketone **65** in the presence of phosphorous pentoxide/methanesulfonic acid.[54b] This reaction presumably involves several [1,5] hydrogen shifts followed by loss of water (eq 15). Certain alkylazulene

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also: (d) Doyle, M. P.; van Leusen D.; Tamblyn, W. H. *Synthesis* **1981**, 787. (e) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919. (f) McKervey, M. A.; Russell, D. N.; Twohig, M. F. *J. Chem. Soc., Chem Commun.* **1985**, 491. (g) Adams, J.; Spero, D. M. *Tetrahedron* **1991**, *47*, 1765. (h) Davies, H. M. L. In *Comprehensive Organic Syntheses*; Trost, B. M., Ed.; Pergamon Press: Oxford, **1991**, Vol. 4, p1031-1065.

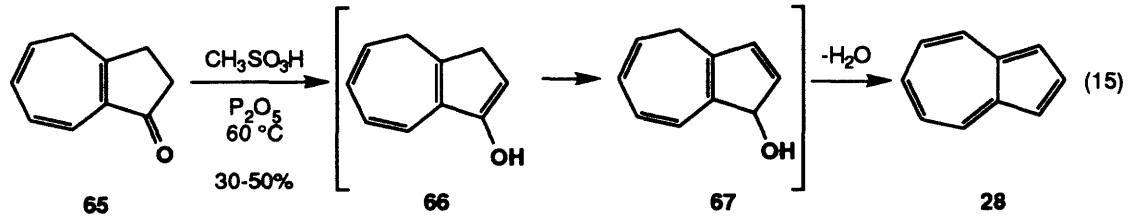
[56]McKervey, M. A.; Tuladhar, S. M.; Twohig, M. F. *J. Chem. Soc., Chem. Commun.* **1984**, 129.

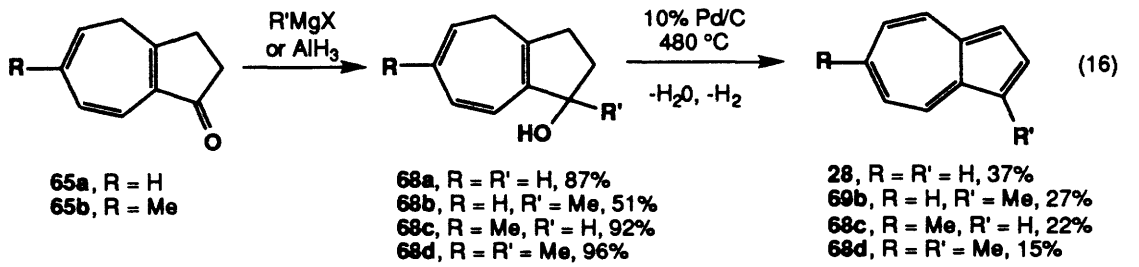
[57](a) Kennedy, M.; McKervey, M. A.; Maguire, A. R.; Tuladhar, S. M.; Twohig, M. F. J. *Chem. Socc. Perkin Trans. 1* **1990**, 1047. (b) Cordi, A. A.; Lacoste, J. -M.; Hennig, P. *J. Chem. Soc Perkin Trans. 1* **1993**, 3.

[58](a) Kennedy, M.; McKervey, M. A. *J. Chem. Soc., Chem. Commun.* **1988**, 1028. (b) Duddeck, H.; Ferguson, G.; Kaitner, B.; Kennedy, M.; McKervey, M. A.; Maguire, A. R. *J. Chem. Soc Perkin Trans. 1* **1990**, 1055.

[59]Scott, L. T.; Sumpter, C. A. *Org. Synth.* **1990**, *69*, 180.

derivatives have also been synthesized from hydroazulenones. Treatment of these ketones with Grignard reagents or hydride sources leads to alcohol derivatives. When subjected to dehydration and dehydrogenation, these intermediates provide azulenes, albeit in low yields (eq 16). The previously described limitations of the dehydrogenative approach also apply to these cases.





65a, R = H
65b, R = Me

68a, R = R' = H, 87%
68b, R = H, R' = Me, 51%
68c, R = Me, R' = H, 92%
68d, R = R' = Me, 96%

28, R = R' = H, 37%
69b, R = H, R' = Me, 27%
68c, R = Me, R' = H, 22%
68d, R = R' = Me, 15%

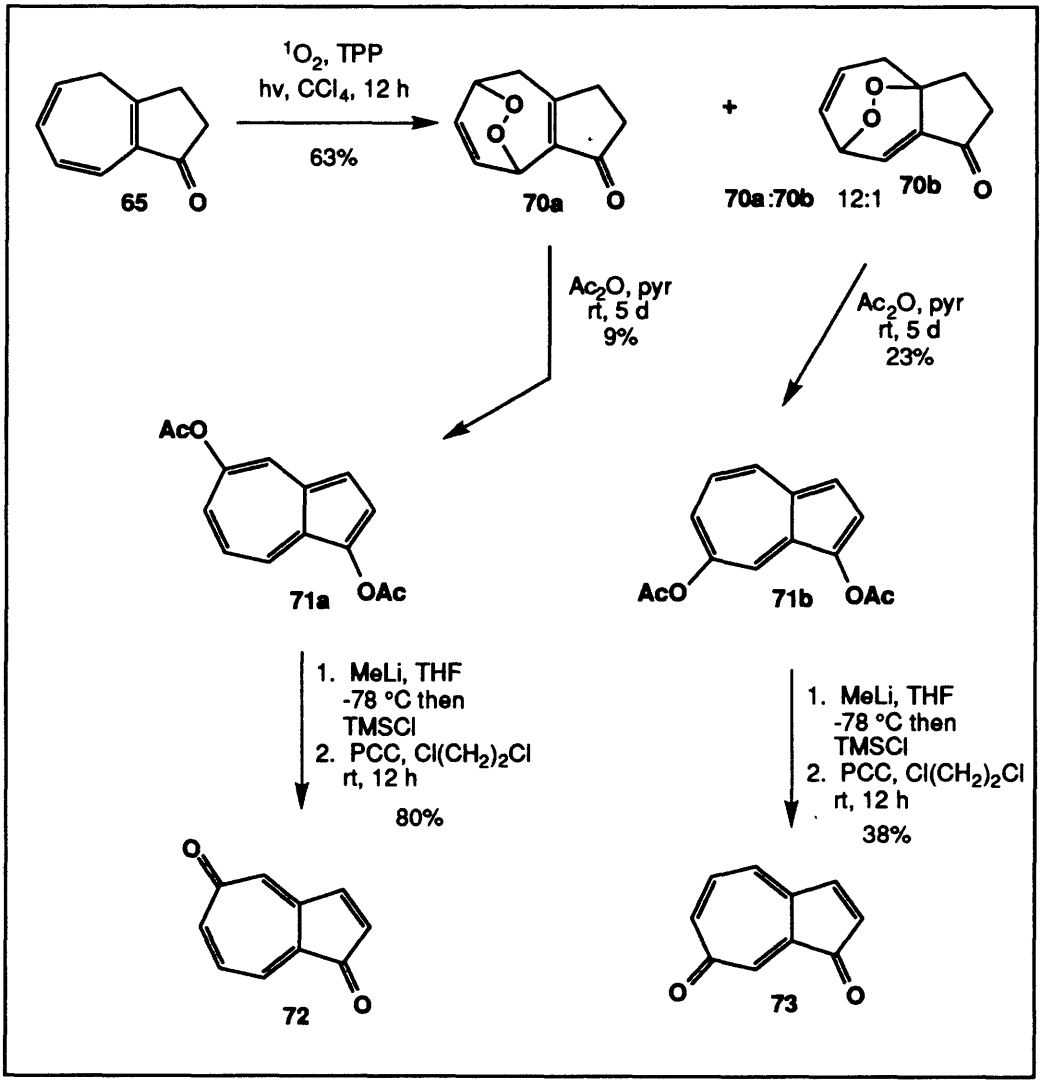
Scott has also used these hydroazulenones to produce the theoretically interesting quinones of azulene.[60] The stable 1,5- and 1,7-azulenoquinones (**72**, **73**) are available as shown in Scheme 7. A [4+2] cycloaddition reaction between **65** and singlet oxygen provides a mixture of the two peroxides **70a-b**, which are then converted to the corresponding 1,5- and 1,7-diacetoxyazulenes (**71a**, **71b**) by a base-induced fragmentation. Conversion of these acetates to the corresponding trimethylsilyl ethers, followed by oxidation with pyridinium chlorochromate provided the quinones as yellow solids (Scheme 7). The more reactive 1,4- and 1,6-azulenequinones have also been

[60](a) Scott, L. T.; Rozeboom, M. D.; Houk, K. N.; Fukunaga, T.; Lindner, H. J.; Hafner, K. *J. Am. Chem. Soc.* **1980**, *102*, 5169. (b) Scott, L. T. *Pure Appl. Chem.* **1983**, *55*, 363.

synthesized from **65**; however, these materials could not be isolated and were trapped with cyclopentadiene.[61]

The previous examples demonstrate that hydrozulenones are generally not useful intermediates for azulene synthesis. The intramolecular Büchner reaction is, however, an excellent method for creating the basic azulene skeleton. If the process could be modified in a manner such that the product formed from this reaction possesses the azulene oxidation state, this approach could become synthetically useful.

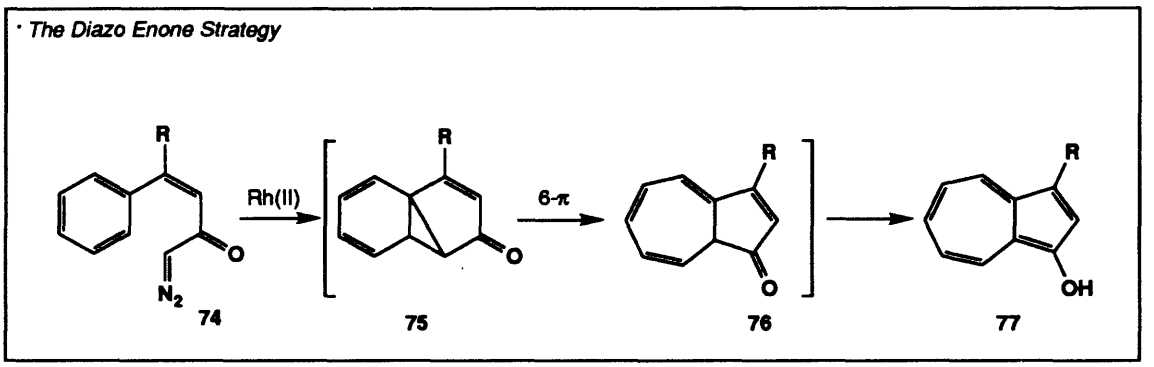
Scheme 7

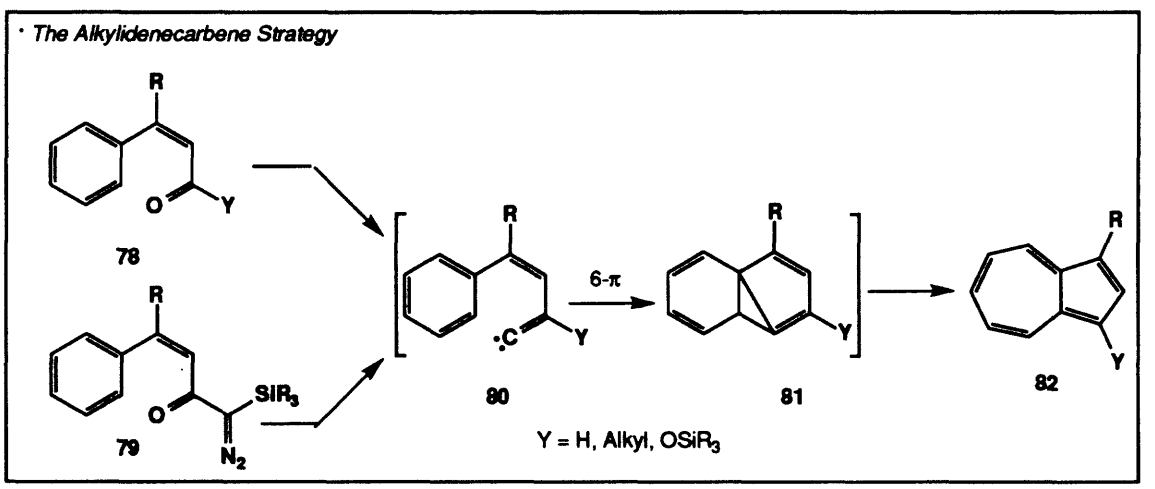


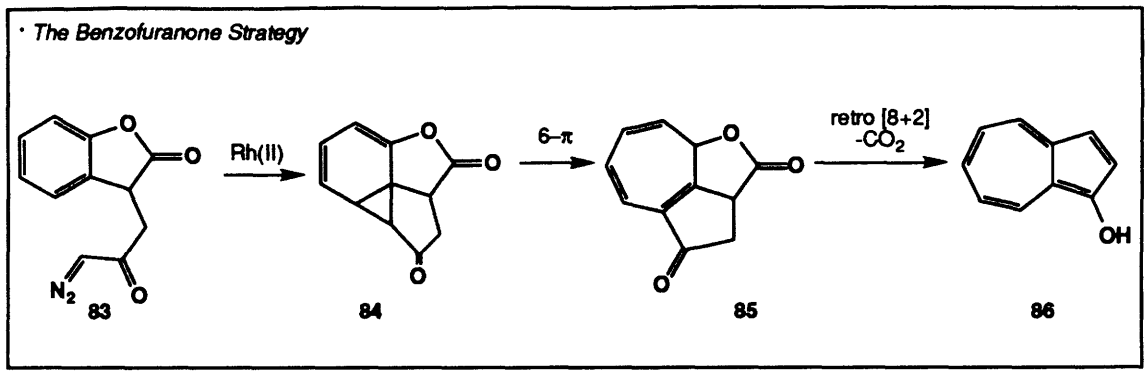
[61]Scott, L. T.; Grütter, P.; Chamberlain, R. E. *J. Am. Chem. Soc.* **1984**, *106*, 4852.

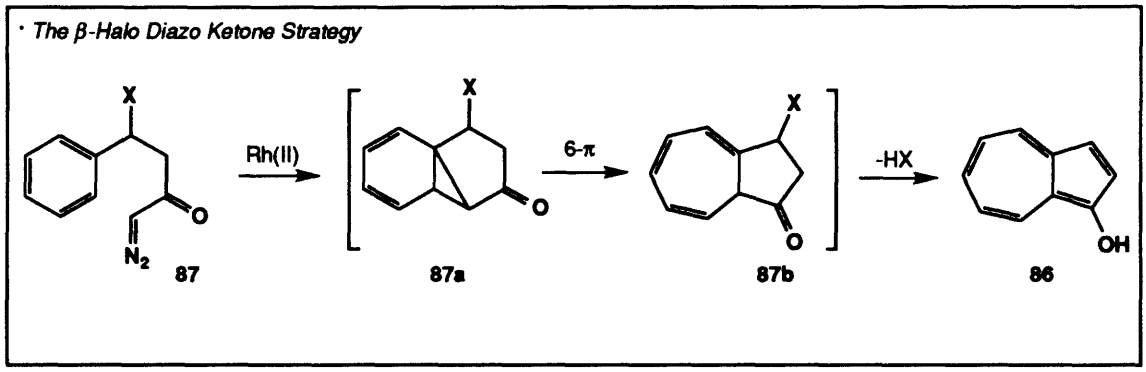
McKervey has already shown that the carbenoid addition is a regioselective process, and it occurs at mild temperatures (*vide supra*). Proper modification of the starting material should allow for an intramolecular Büchner reaction which generates azulenes. Outlined below, then, are several of the strategies which have been investigated in our laboratories.

Scheme 8





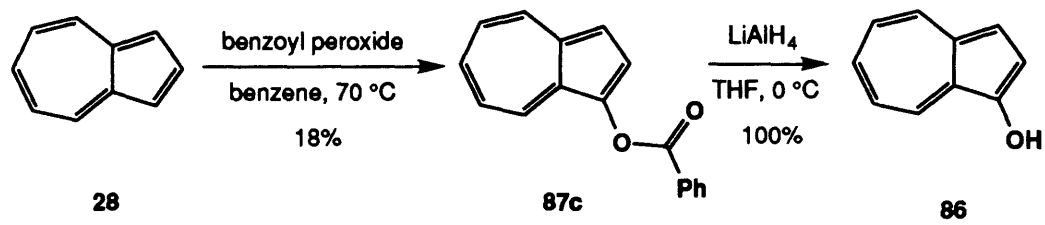




The approaches outlined above have several appealing features. Note that in all of these proposed reaction schemes azulenes would be formed under mild conditions either directly or by simple tautomerization of a corresponding azulenone, presumably with excellent regiochemical control. An interesting feature of most of these reactions is that they provide access to 1-hydroxyazulenes, a relatively unknown class of azulenes. In 1989, Asao and co-workers reported the first synthesis of 1-hydroxyazulene.[62] Treatment of azulene (**28**) with benzoyl peroxide followed by reduction with lithium aluminum hydride provided a green oil corresponding to the desired product **86** (eq 17). 3-Hydroxyguaiazulene (**88**) was produced in a similar manner. While other hydroxyazulenes (such as the 2- and 6-substituted derivatives) behave in a fashion similar to naphthols and phenols, 1-hydroxyazulenes are remarkably different. Both **86** and **88**

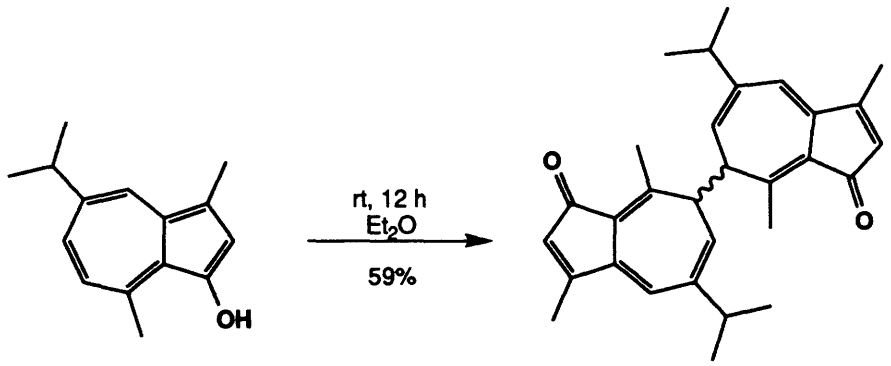
[62](a) Asao, T.; Ito, S.; Morita, N. *Tetrahedron Lett.* **1989**, *30*, 6693. (b) Asao, T. *Pure Appl. Chem.* **1990**, *62*, 507.

were stable in solution at -30 °C, but rapidly decomposed upon warming to room temperature.



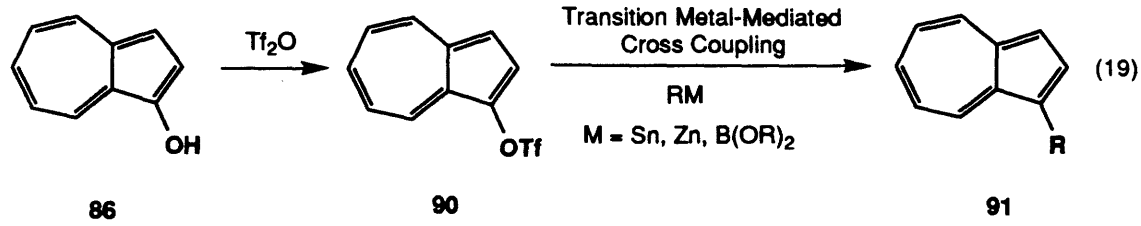
28 87c 86 (17)

The mechanism by which these materials decompose appears to involve phenolic-type oxidation.[62b] While only polymeric material is obtained from the unsubstituted case, 3-hydroxyguaiazulene (**88**) dimerizes on standing in diethyl ether at room temperature (eq 18). More detailed information on the properties and reactivities of these interesting derivatives is not available due to a lack of general methods for their synthesis. Our approaches (*vide infra*) would potentially allow access to a variety of functionalized derivatives which should broaden the knowledge of this class of azulenes.



88 89 (18)

The fact that our proposed azulene syntheses lead to 1-hydroxyazulene derivatives has one other important benefit. Proper functionalization of the hydroxyazulene should allow for further elaboration of the azulene nucleus. For instance, we anticipate that the corresponding triflates (**90**) should undergo transition metal-mediated cross coupling reactions, thereby extending the utility of the new process (eq 19).



86 90 91 (19)

In the next two chapters, each of the new proposals will be presented and critically discussed, culminating in the development of a new ring expansion-annulation approach to substituted azulenes.

CHAPTER 2

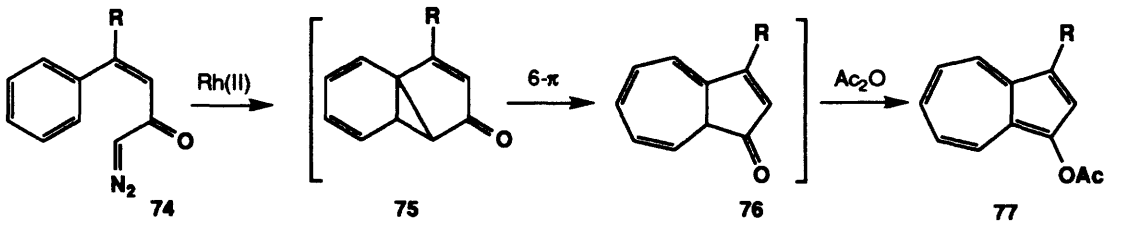
Ring Expansion-Annulation Approaches to Substituted Azulenes: Part I

The Diazo Enone Strategy

The diazo enone strategy (Scheme 9) seemed to be the most logical starting point for our studies on the synthesis of substituted azulenes via modified intramolecular Büchner reactions. Recall that this is one of several approaches which generates azulenes via a keto-enol tautomerization in the final step of the reaction cascade. Note that for this reaction to succeed, the aryl ring and diazo ketone moiety must have a *cis* relationship about the double bond of the substrate. Two straightforward model cases were developed to study this proposed method.

Scheme 9

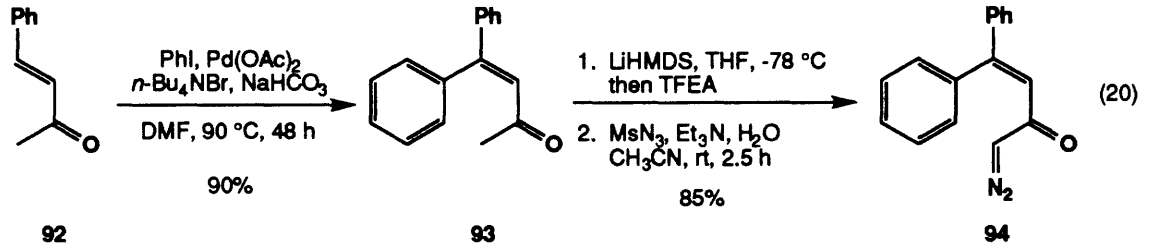
· The Diazo Enone Strategy

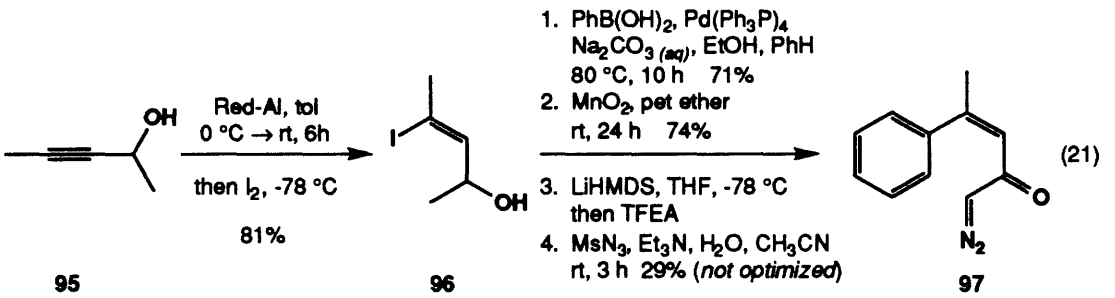


For the purpose of establishing the feasibility of the proposed process, we decided the easiest way to insure the requisite *cis* relationship between the two reactive sites would be by employing the β,β-diphenyl substituted derivative **93**.[63] Ronald Brisbois in our laboratories achieved an efficient synthesis of this material by the reaction of 4-phenyl-3-

[63]Tsuji, J.; Nagashima, H. *Tetrahedron* **1984**, *40*, 2699.

buten-2-one (**92**) with iodobenzene under modified Heck conditions.[64] The diazo ketone **94** was then produced by a diazo group transfer procedure previously developed in our laboratories (eq 20).[65] Hiroo Koyama developed a short synthesis of a similar model compound **97**. Starting from propargylic alcohol **95**,[66] the vinyl iodide **96**[67] is produced by hydroalumination of the alkyne and quenching with iodine.[68] Conversion of the iodide to **97** was accomplished by Suzuki coupling,[69] oxidation with manganese dioxide, and diazo group transfer (eq 21).





As shown in Scheme 10, the ring expansion-annulation reaction of Brisbois' substrate confirmed the feasibility of the diazo enone strategy; 1-hydroxyazulene derivatives could be made via this route. Exposure of **94** to a catalytic amount of rhodium(II) acetate in refluxing dichloromethane, followed by trapping the unstable 1-

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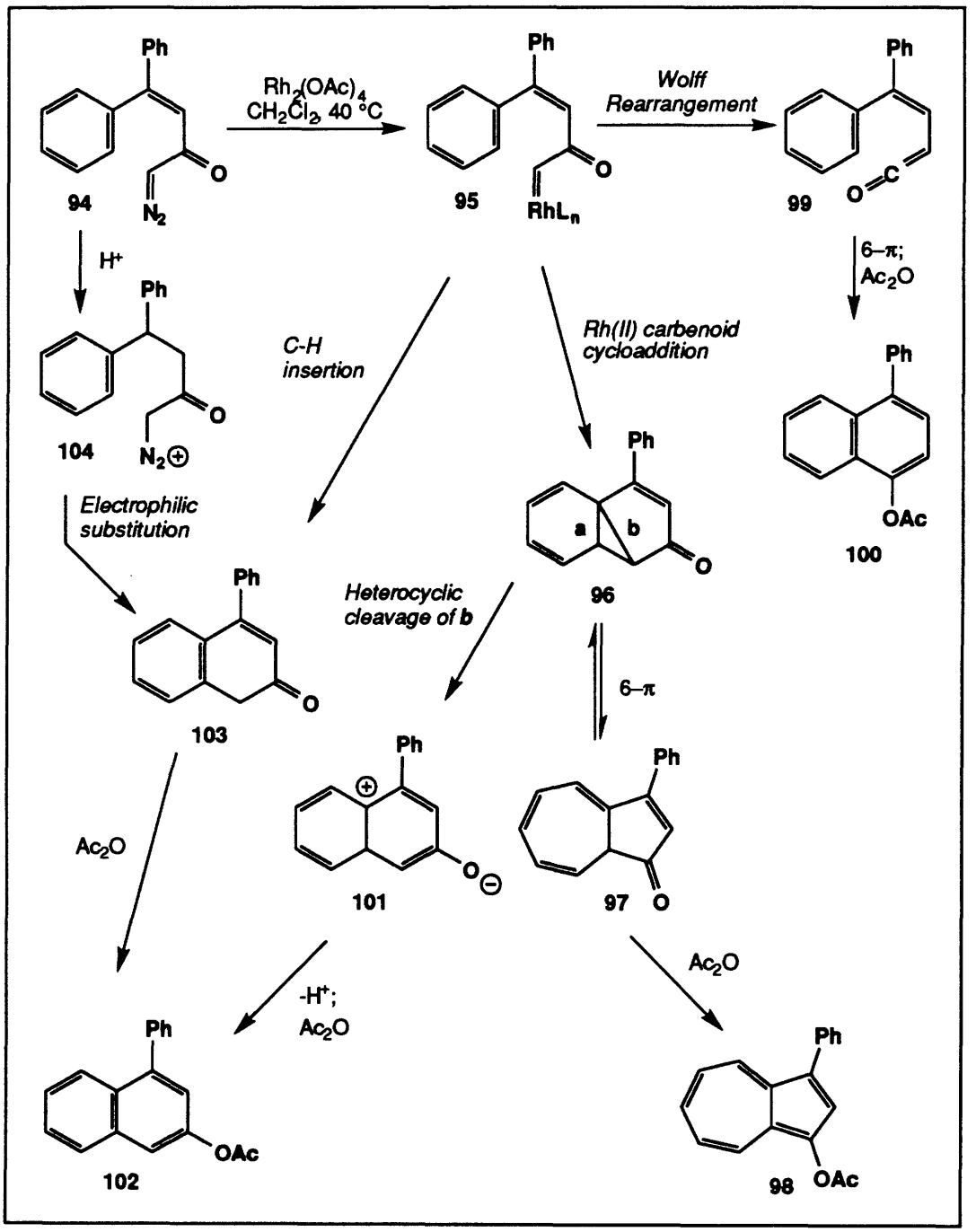
[64]Jeffery, T. *Synthesis* **1987**, 70.
[65]Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959.
[66]This material was prepared in 70% yield by reaction of propynylmagnesium bromide with acetaldehyde.
[67]Cowell, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4193.
[68]Corey, E. J.; Katzenellenbogen, J. A.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 4245.
[69]For a recent review of the Suzuki reaction, see: Suzuki, A. *Pure App. Chem.* **1991**, *63*, 419.

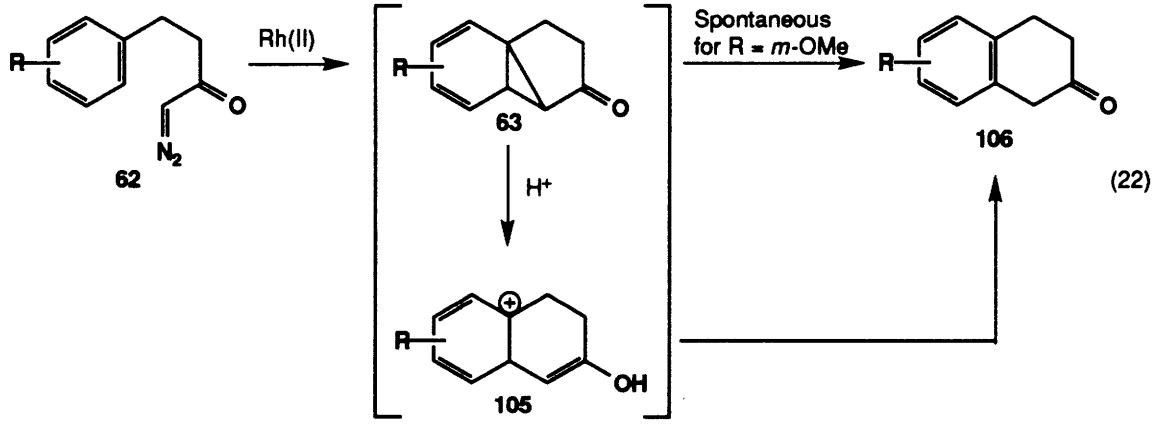
hydroxyazulene (*vide supra*) with acetic anhydride furnished 1-acetoxy-3-phenylazulene (**98**) as a stable blue compound. Unfortunately, this reaction gave near quantitative

Scheme 10



conversion of starting material to a mixture of the desired azulene and two isomeric products, the α- and β-naphthol acetates **100** and **102**. Separation of these three compounds proved to be very difficult. Similar results were obtained with Koyama's substrate.

Possible mechanisms to explain the formation of each product is outlined above in Scheme 10. The desired azulene arises from the expected intramolecular Büchner reaction pathway via **96**. Electrocyclic cleavage of bond **a** in intermediate **96** then gives azulenone **97**, which tautomerizes and is trapped as its acetate. The β-naphthol byproduct **102** can arise by insertion of the rhodium carbenoid into an aryl C-H bond.[70] Alternatively, intermediate **96** can also be a precursor to **102**. McKervey has previously shown that heterolytic cleavage of similar intermediates can occur in the presence of a catalytic amount of trifluoroacetic acid, or in certain cases, spontaneously, to provide β-tetralones (eq 22). Analogous heterolytic cleavage of **96** could produce **101** and then the β-naphthol derivative **102**. Finally, the presence of traces of acid could also lead to **102** via electrophilic attack of diazonium ion **104** on the aromatic ring.

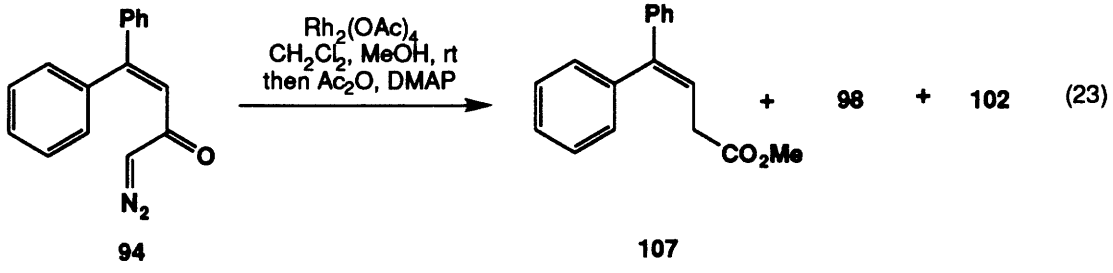


(22)

The formation of α-naphthol **100** appears to proceed via a rhodium carbenoid mediated thermal Wolff rearrangement. This hypothesis is supported by the following experimental evidence. Treatment of diazo ketone **94** with rhodium(II) acetate in the

[70]For reviews of C-H insertion, see: Maas, G. *Top. Curr. Chem.* **1987**, *137*, 75 and ref. 55g.

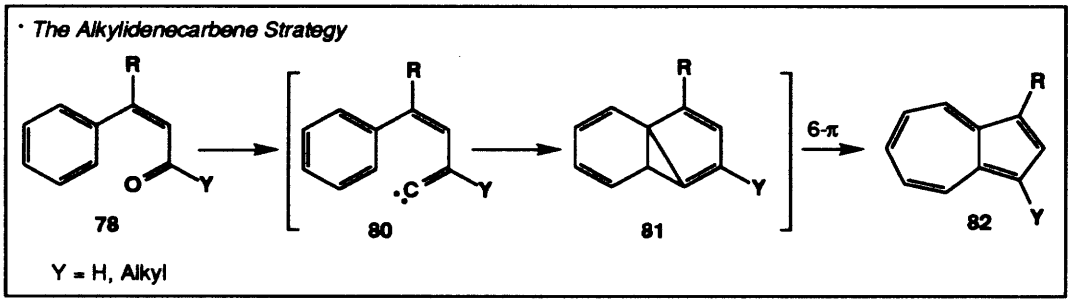
presence of 100 equivalents of methanol resulted in the formation of ester **107**, along with the azulene **98** and β-naphthol **102** (eq 23). This result strongly suggests that dienylketene **99** is formed under the reaction conditions and is the intermediate responsible for producing **100**.[71] Unfortunately, little progress has been subsequently made in improving the efficiency of this diazo enone approach to substituted azulenes. In spite of considerable efforts, Brisbois and Koyama were unable to suppress the side reactions leading to the formation of the naphthol byproducts. It was clear that new routes would have to be developed to circumvent these problems.



The Alkylidenecarbene Strategies

In seeking to develop alternatives to the diazo enone strategy, we became interested in the potential utility of another carbene species, the alkylidenecarbenes, as intermediates

Scheme 11



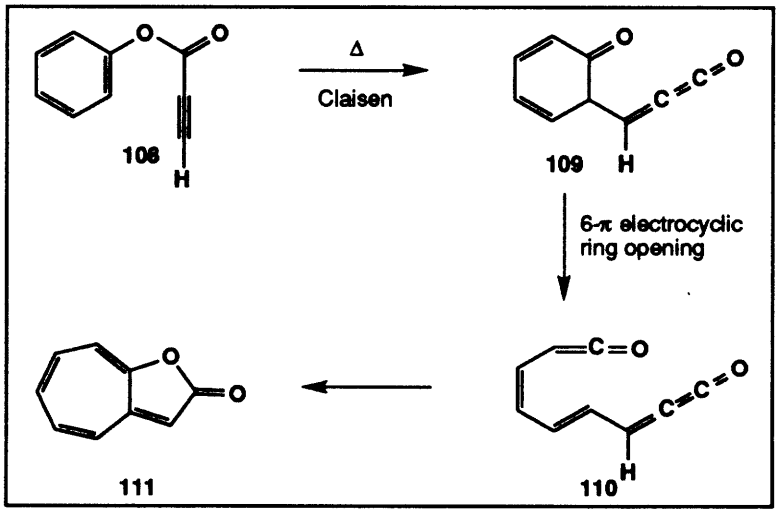
[71]A similar rhodium carbenoid mediated thermal Wolff rearrangements has been reported. See Taylor, E. C.; Davies, H. M. L. *Tetrahedron Lett.* **1983**, *24*, 5453.

in intramolecular Büchner-type ring expansion-annulations leading to substituted azulenes (Scheme 11). This strategy was viewed as potentially very attractive since, as summarized below, a number of different methods are available for the generation of alkylidenecarbenes.

Generation of Alkylidenecarbenes via Flash Vacuum Pyrolysis

One of the earliest reports involving the generation of alkylidenecarbenes involved flash vacuum pyrolysis (FVP) and came from the laboratories of Trahanovsky (Scheme 12). This group demonstrated that treatment of aryl propiolates under FVP conditions resulted in the formation of cyclohepta[b]furan-2-ones (e.g., **111**) in moderate yields.[72] It should be noted, however, that their proposed mechanism did not involve an alkylidenecarbene intermediate. Rather, Trahanovsky suggested a Claisen rearrangement of phenyl propiolate (**108**) to give **109** as the initial step in this process. Intermediate **109** was then believed to undergo electrocyclic ring opening and subsequent cyclization to provide furanone **111**.

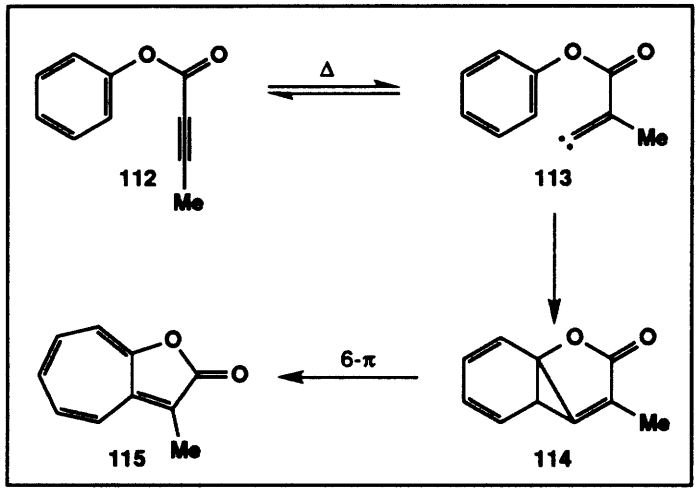
Scheme 12



[72]Trahanovsky, W. S.; Emeis, S. L.; Lee, A. S. *J. Org. Chem.* **1976**, *41*, 4044.

Several years later, however, Brown and coworkers reexamined this reaction.[73] Instead of an initial Claisen rearrangement, these researchers believed that formation of alkylidenecarbene **113** was the first step in the mechanism leading to the bicyclic furanone (Scheme 13). The alkylidenecarbene was then suggested to undergo a Büchner-like reaction with the aromatic ring leading to tricyclic lactone **114**, which provided the product via 6-π electrocyclic ring opening. Their proposal was supported by previous studies in Brown's group on the mechanism of certain acetylene isomerizations.[74] By subjecting ^{13}C-labeled phenylacetylene (**116**) to the conditions of FVP, a 1:1 ratio of radiolabeled products was obtained, presumably via an alkylidenecarbene intermediate (eq 24). Brown and co-workers have also demonstrated that alkylidenecarbenes can be generated from alkyl propiolates[75] and Meldrum's acid derivatives,[71] and shown that these intermediates will

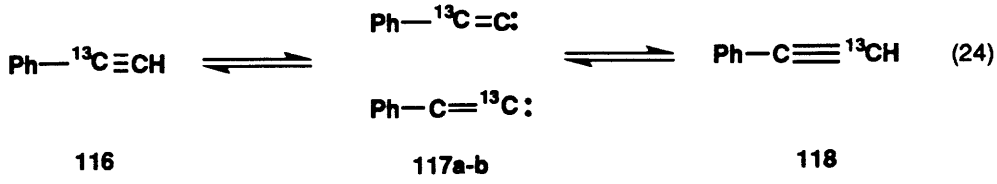
Scheme 13



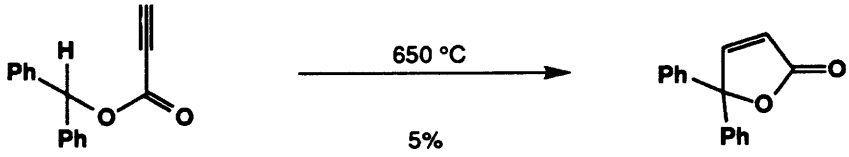
undergo typical carbene reactions, including Büchner-type reactions to form azulenes (eq 25 and 26). However, while it is clear that alkylidenecarbenes can be generated under FVP

[73]Brown, R. F. C.; Eastwood, F. W. *J. Org. Chem.* **1981**, *46*, 4588.
[74]Brown, R. F. C.; Eastwood, F. W.; Harrington, K. J.; McMullen, G. L. *Aust. J. Chem.* **1974**, *27*, 2393.
[75](a) Brown, R. F. C.; Eastwood, F. W.; Jackman, G. P. *Aust. J. Chem.* **1977**, *30*, 1757. (b) Brown, R. F. C.; Eastwood, F. W.; Chaichit, N.; Gatehouse, B. M.; Pfeiffer, J. M.; Woodroffe, D. *Aust. J. Chem.* **1981**, *34*, 1467.

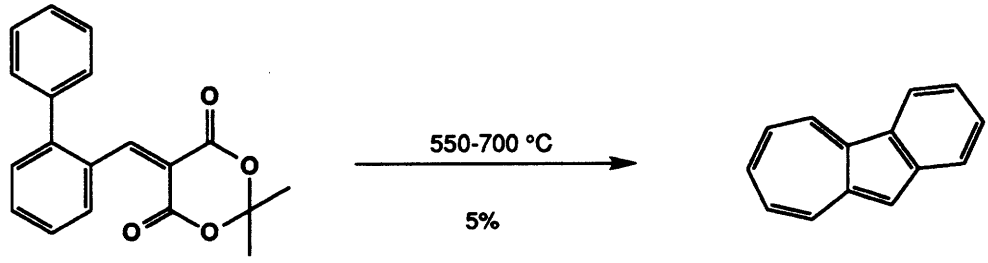
conditions, we did not view this approach as a synthetically useful method for their production.



(24)



(25)



(26)

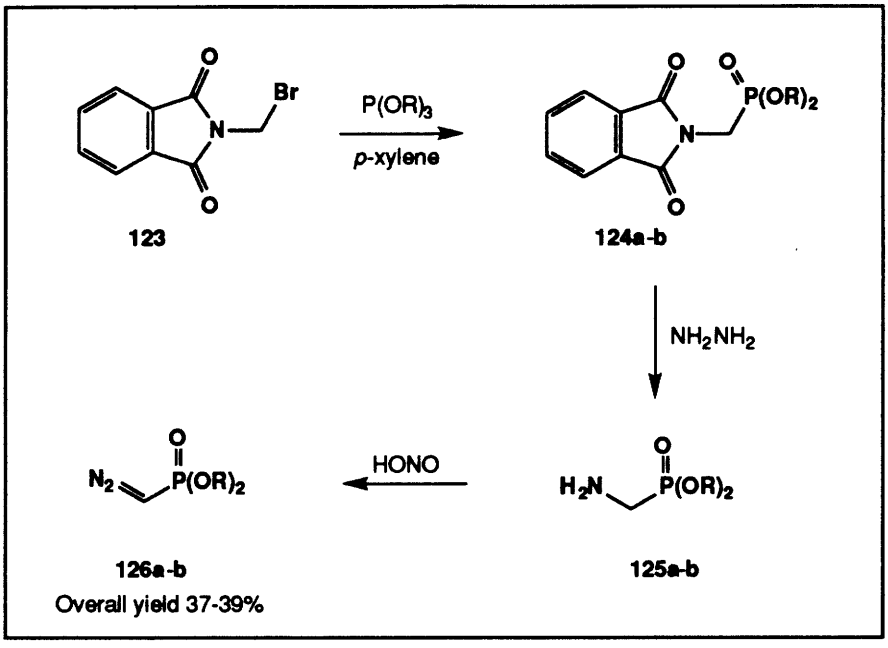
Generation of Alkylidenecarbenes via Diazomethylphosphonates

Alkylidenecarbenes can be generated under more synthetically useful conditions, most notably by the reaction of carbonyl compounds with diazomethylphosphonate (DAMP) reagents. These reagents were first synthesized in the early 1970s by Seyferth and Regitz via multistep procedures as illustrated in Scheme 14.[76] An Arbuzov reaction of bromide **123** with trialkylphosphites gave the phosphonates **124**. Conversion of these compounds to diazomethylphosphonates **126** was accomplished by treatment with

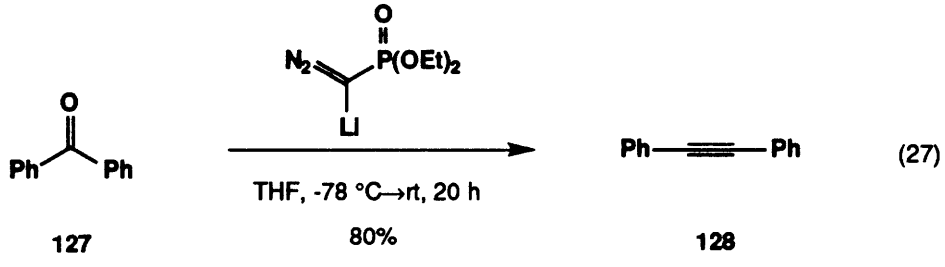
[76](a) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1380. (b) Regitz, M. *Liebigs Ann. Chem.* **1971**, *748*, 207.

hydrazine, followed by diazotization of the resulting α-aminophosphonates with nitrous acid. The desired diazophosphonates were isolated as stable yellow oils in low to moderate yields.

Scheme 14



In 1973, Colvin and Hamill demonstrated a new method for generating alkylidenecarbenes by the reaction diazomethylphosphonates with aryl ketones and aldehydes.[77] For example, metalation of **126b** with *n*-BuLi at -78 °C in tetrahydrofuran gave the lithium derivative, which upon the addition of benzophenone provided diphenylacetylene (**128**) in 80% yield (eq 27).

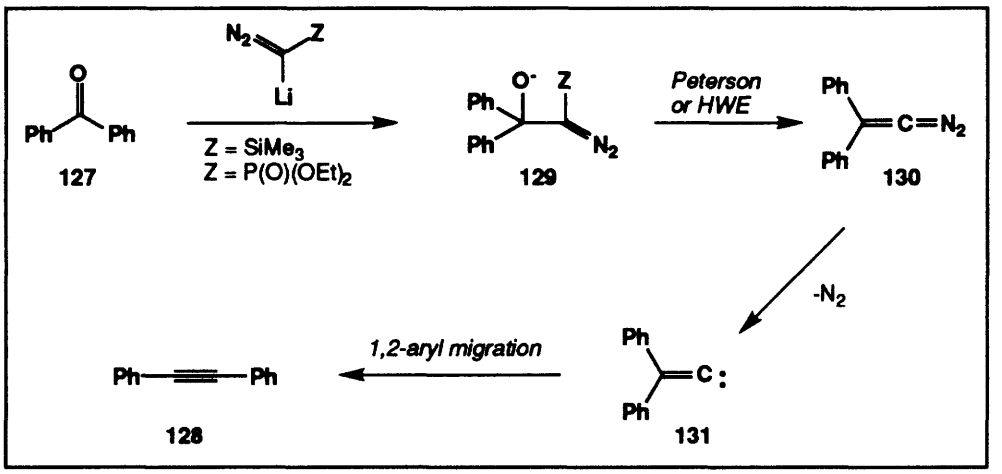


(27)

[77](a) Colvin, E. W.; Hamill, B. J. *J. Chem. Soc., Chem. Commun.* **1973**, 151. See also (b) Colvin, E. W.; Hamill, B. J. *J. Chem. Soc. Perkin Trans. 1* **1977**, 869.

Colvin also found that a similar reaction occurred between the lithium anion of (trimethylsilyl)diazomethane and benzophenone.[74] It is likely that these reactions share a common mechanism; outlined in Scheme 15 is the probable course for both. Condensation of either lithium derivative leads to the addition product **129**. The formation of the vinyl diazo compound **130**, a common intermediate for both reactions, can then occur by either a Peterson or HWE-type collapse of **129**. The acetylene **128** then can arise from α-elimination of nitrogen from **130**, followed by rearrangement of the resulting alkylidenecarbene **131**.

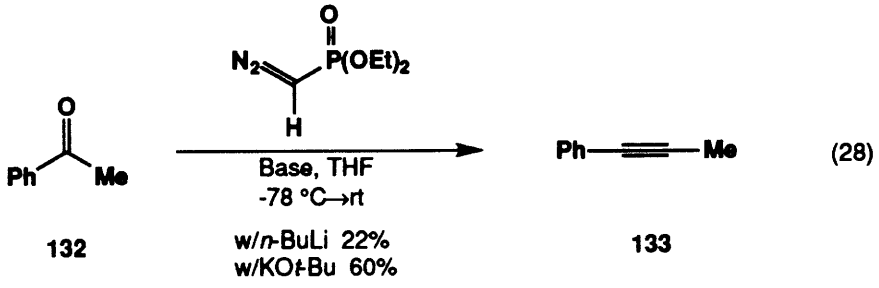
Scheme 15



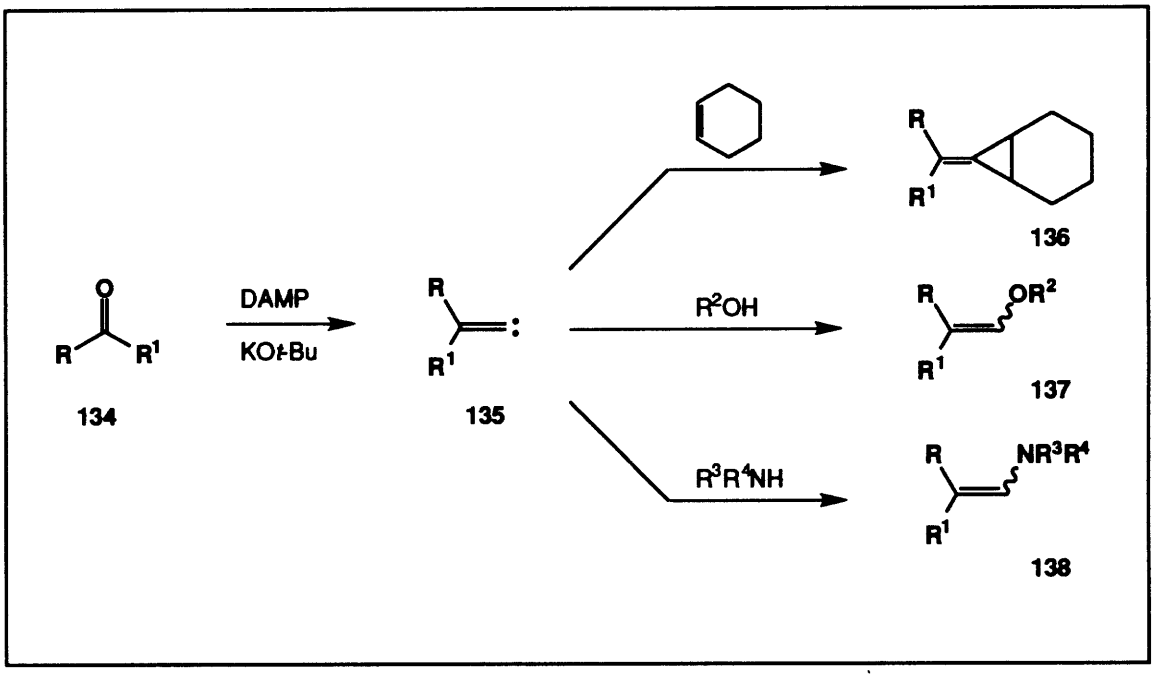
Several years after Colvin's initial studies, Gilbert and coworkers reported an improvement to this method.[78] Under the originally reported conditions for this reaction (*n*-BuLi as the base), Colvin found the scope of the process to be limited to non-enolizable ketones and aldehydes. By employing potassium *t*-butoxide as the base, however, the reaction becomes quite general (eq 28). Gilbert has also reported that the intermediate alkylidenecarbenes can be trapped by suitable reagents. For example, when alkenes,[79]

[78](a) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1979**, *44*, 4997. (b) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1982**, *47*, 1837.
[79]Gilbert, J. C.; Weerasooriya, U.; Giamalva, D. *Tetrahedron Lett.* **1979**, 4619.

alcohols,[80] or amines are included in the reaction mixture,[76] the carbene can be intercepted to form cyclopropanes, enol ethers, or enamines in good to excellent yields (Scheme 16).



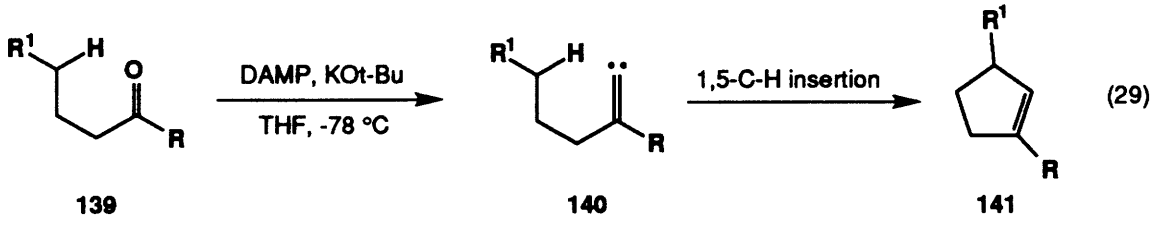
Scheme 16



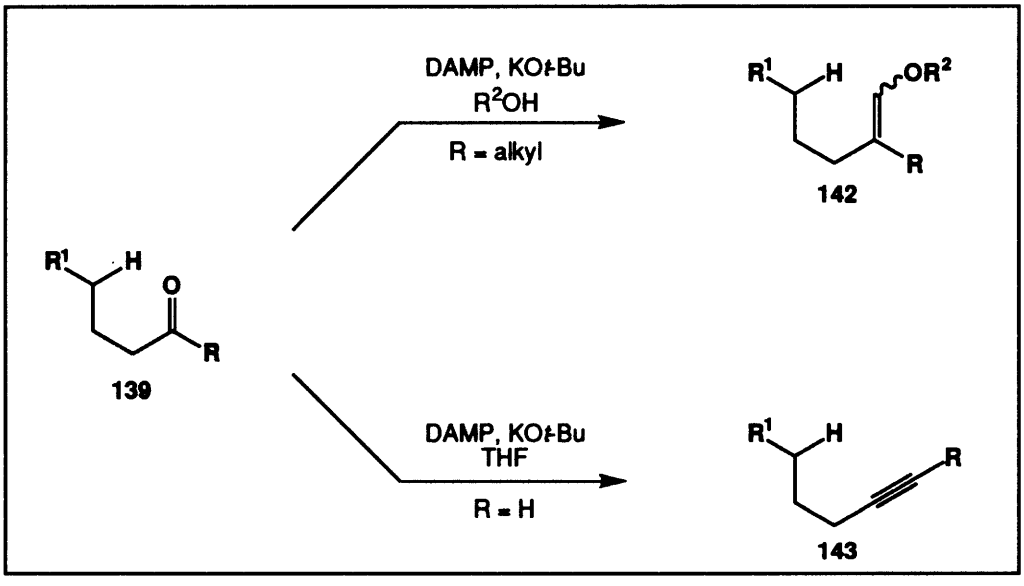
Most importantly, alkylidenecarbenes generated under these conditions are also capable of undergoing intramolecular reactions to form cyclic products. For example, the reaction of the DAMP reagent with dialkyl ketones possessing γ-hydrogens leads to the

[80]Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1983**, *48*, 448.

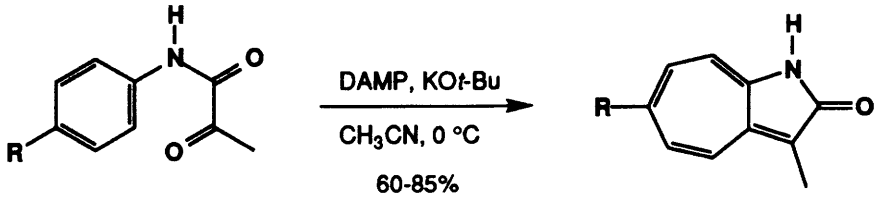
formation of cyclopentenes in moderate to excellent yields (eq 29).[81] As shown in Scheme 17, the production of cyclopentenes, however, cannot compete with intermolecular trapping by a protic solvent (such as methanol) or with an intramolecular 1,2-hydrogen shift.[77] In 1986, Gilbert reported that intramolecular Büchner reactions of alkylidenecarbenes were also possible.[82] The reaction of various 2-oxopropanamides **144a-c** with the DAMP reagent in acetonitrile was found to lead to the formation of substituted cyclohepta[b]pyrrolo-2-ones in good yields (eq 30). Based on this report and the earlier work of Brown (*vide supra*), it seemed likely that our proposed alkylidenecarbene-based plan for azulene synthesis (Scheme 11) would be feasible.



Scheme 17



[81]Gilbert, J. C.; Giamalva. D. H.; Weerasooriya, U. *J. Org. Chem.* **1983**, *48*, 5251. Also see ref. 75.
[82]Gilbert, J. C.; Blackburn, B. K. *J. Org. Chem.* **1986**, *51*, 4087.



(30)

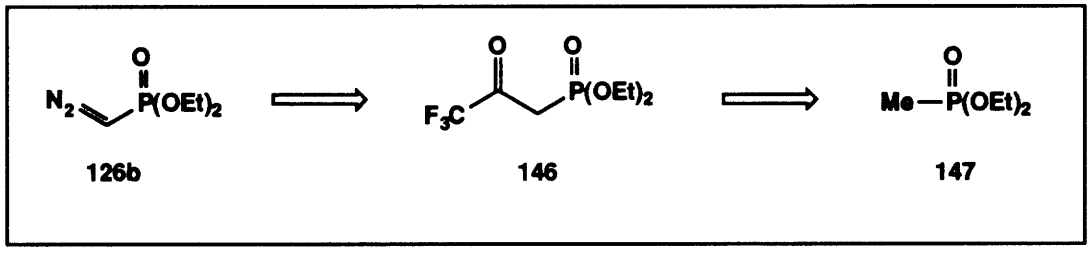
R = H, **144a**
R = Me, **144b**
R = Cl, **144c**

R = H, **145a**
R = Me, **145b**
R = Cl, **145c**

Initial Studies

In order to investigate the feasibility of the proposed alkylidenecarbene route to substituted azulenes, we required convenient access to significant quantities of the DAMP reagent which is not commercially available. We felt that the known multistep routes of Seyferth and Regitz were cumbersome and wondered if our detrifluoroacetylative diazo group transfer procedure could be applied to the commercially available phosphonate **147** (Scheme 18). While several other research groups have reported the synthesis of DAMP reagents via diazo group transfer strategies, most of these procedures are no shorter (3-4 steps) than the original Seyferth/Regitz routes, and they produce the reagent in similar modest overall yield.[83]

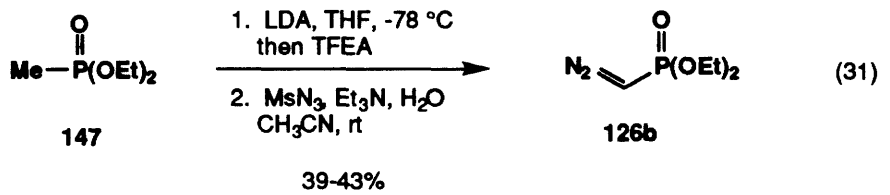
Scheme 18



126b **146** **147**

[83](a) Regitz, M.; Anschütz, W.; Liedhegener, A. *Chem. Ber.* **1968**, *101*, 3734. (b) Regitz, M.; Anschütz, W. *Liebigs Ann. Chem.* **1969**, *730*, 194. (c) Tomioka, H.; Toriyama, N.; Izawa, Y. *J. Org. Chem.* **1977**, *42*, 552. (d) Khare, A. B.; McKenna, C. E. *Synthesis* **1991**, 405.

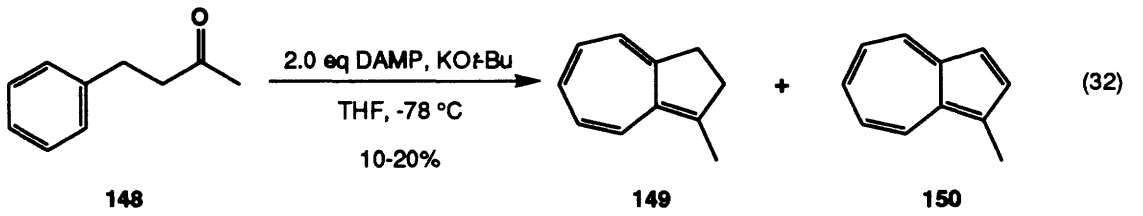
We found that the application of our diazo transfer method allows the production of the DAMP reagent in multigram quantities in two steps as outlined in eq 31. The trifluoroacetyl intermediate **146** is not purified, and in fact if desired, the sequence can probably be carried out as a "one-pot" operation. While the overall yield for this process is not significantly better than prior methods, the ease of this sequence makes it more attractive than any previously reported routes. It is also possible that the yield of this preparation can be significantly improved since little effort has been devoted to optimizing this procedure.



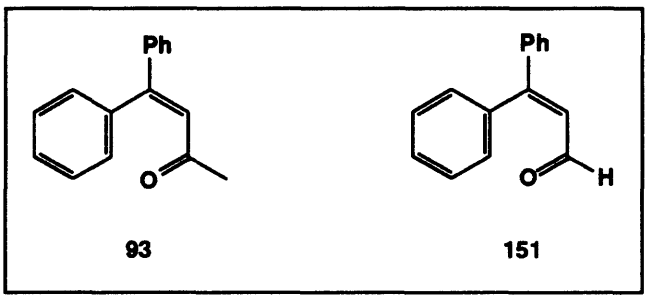
(31)

To test the feasibility of the proposed azulene synthesis, Koyama initially examined the reaction of benzylacetone (**148**) with the DAMP reagent with the expectation that if. successful, this reaction would provide a dihydroazulene. Note that, this substrate lacks a double-bond as compared to the enone intermediate described above (Scheme 11). When **148** was treated with the DAMP reagent, low to moderate yields of the dihydroazulene **149** as well as the fully oxidized azulene **150** were isolated from the reaction mixture (eq 32). While this was an encouraging result, our goal from the outset of this project was to avoid methods which require a separate dehydrogenation step. Therefore, several new model substrates that would provide azulenes directly were chosen (Scheme 19). Since these unsaturated substrates again require a *cis* relationship between the two reactive centers, the same model system used by Brisbois in the diazo enone strategy was chosen, along with enal derivative **151.**[84]

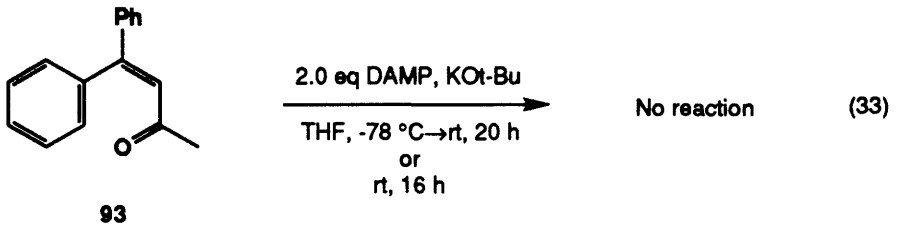
[84]The enal was produced in 85% yield by the reaction of cinnamaldehyde with iodobenzene under the modified Heck reaction conditions described in Jeffery. See ref 63.



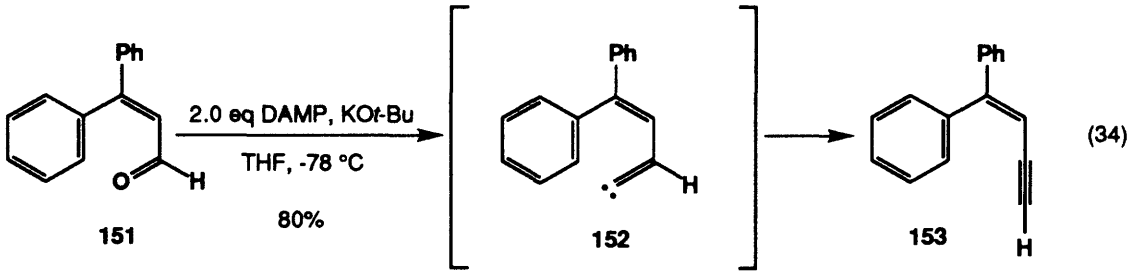
Scheme 19



Initial studies involved reaction of **93** and **151** with the DAMP reagent under various conditions. Treatment of enone **93** with the DAMP reagent and potassium *t*-butoxide in tetrahydrofuran at -78 °C did not lead to azulene formation. Allowing the reaction to warm to room temperature over 20 h also did not produce azulenes, and only enone starting material was recovered from the reaction mixture (eq 33). Conducting the reaction at 25 °C from the outset again lead only to recovered enone. These results, while disappointing, were not totally unexpected. Gilbert had previously reported that α,β-unsaturated ketones are poor substrates for reaction with the DAMP reagent due to their relatively low electrophilic character. In these cases, the DAMP reagent tends to undergo self condensation faster than addition to the carbonyl group.



Not surprisingly, enal **151** also did not produce azulenes when treated with the DAMP reagent. In this case, the reaction of **151** with the diazomethylphosphonate reagent did lead to an alkylidenecarbene. This intermediate, however, underwent rapid 1,2-hydrogen shift to give enyne **153** as the sole product (eq 34). Recall that Gilbert observed a similar trend for aldehydes; 1,2-hydrogen shifts occurred much faster than competing reactions such as C-H bond insertion. It is clear that strategies based on alkylidenecarbenes generated from aldehydes stand little chance of providing azulenes via Büchner reactions. Enones, however, were still viewed as useful precursors to azulenes provided that conditions for generating the necessary alkylidenecarbenes were available. Fortunately, such a method had previously been reported.



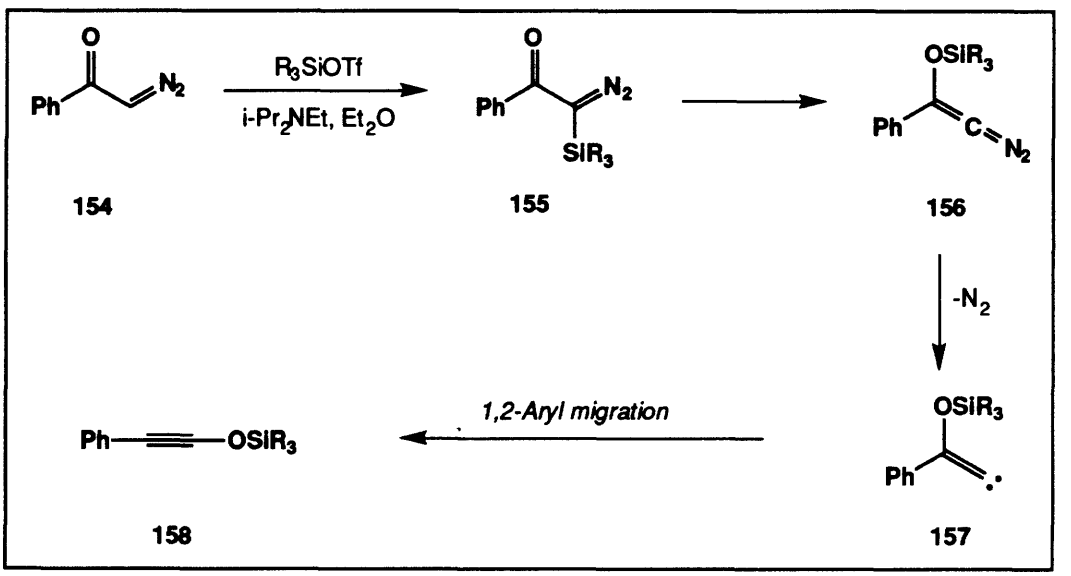
Generation of Alkylidenecarbenes via α-Silyldiazo ketones

The ability of α-silyldiazo ketones to rearrange to alkylidenecarbenes was first demonstrated by Maas and Brückmann.[85] These researchers observed that the reaction of

[85]Maas, G.; Brückmann, R. *J. Org. Chem.* **1985**, *50*, 2801.

aryl diazo ketones such as **154** with trialkylsilyl triflates leads to the formation of α-silylated diazo ketones. IR analysis of the crude reaction mixture, however, indicated the presence of an acetylene derivative along with the desired product. By allowing the crude α-silyldiazo ketone to stand at room temperature for several hours, complete conversion to the acetylene was observed. This mysterious alkyne was eventually determined to be a siloxyacetylene derivative which Maas and Brückmann viewed as arising from a thermal 1,3-C→O silyl shift with a loss of nitrogen to generate a siloxyalkylidenecarbene species (Scheme 20). Related alkylidenecarbenes had been previously shown to rearrange to acetylenes by 1,2-aryl migration (*vide supra*).

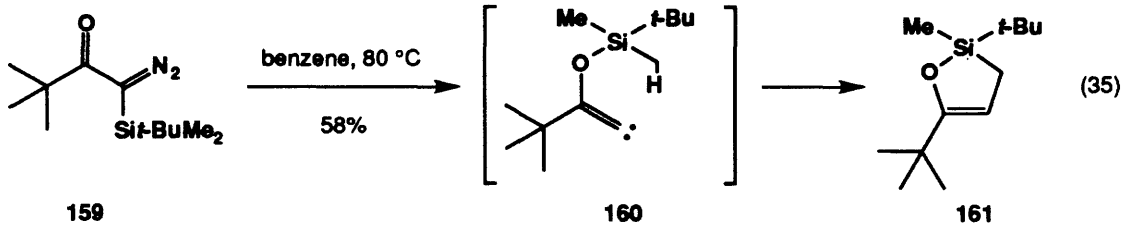
Scheme 20



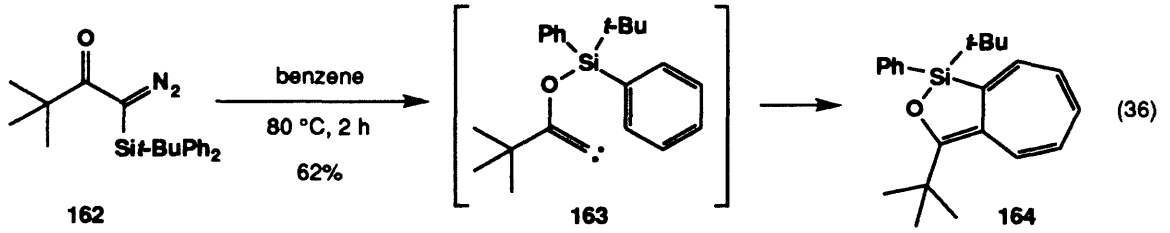
Two years later, Maas and Brückmann reported that alkyl diazo ketones could also be silylated with trialkylsilyl triflates.[86] These compounds, however, tended to be more stable at room temperature than their corresponding aryl counterparts. Rearrangement of the alkyl silyldiazo ketones occurred readily in refluxing benzene to give siloxyalkylidenecarbenes. The fate of these carbenes, though, was quite different from that

[86]Brückmann, R.; Maas, G. *Chem. Ber.* **1987**, *120*, 635.

of the aryl substituted derivatives. Unlike their aryl counterparts, alkyl groups generally do not undergo a facile 1,2-migration; thus, no siloxyacetylenes are formed on thermolysis of these alkyl silyldiazo ketones. Rather, carbene insertion into a C-H bond occurred, generating cyclic silyl enol ethers such as **161** (eq 35). By altering the substituents on the Si atom, the alkylidenecarbene can be coerced into reactions other than C-H insertion. For example, the thermolysis of **162**, in which there are no suitable C-H bonds for carbene insertion, lead to the formation of heptafulvene **164** via a Büchner-type reaction (eq 36).[87]



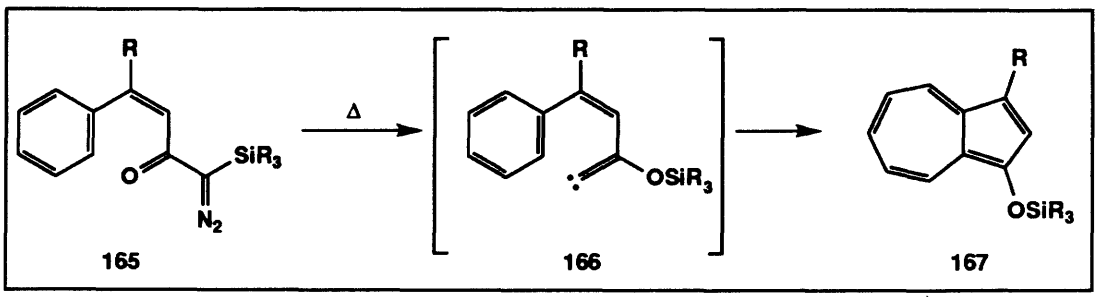
159 160 161



162 163 164

This report lead us to wonder if silyldiazo enone **165** would participate in a similar Büchner reaction to give azulenes (Scheme 21). This proposal could be easily tested with

Scheme 21

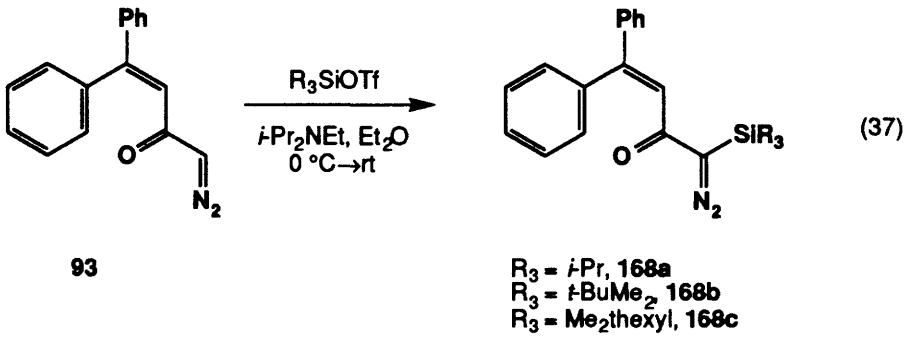


165 166 167

[87]Brückmann, R.; Maas, G. *J. Chem. Soc., Chem. Commun.* **1986**, 1782.

the substrates developed by Brisbois and Koyama for the diazo enone strategy, and would, if successful, provide direct access to protected 1-hydroxyazulenes.

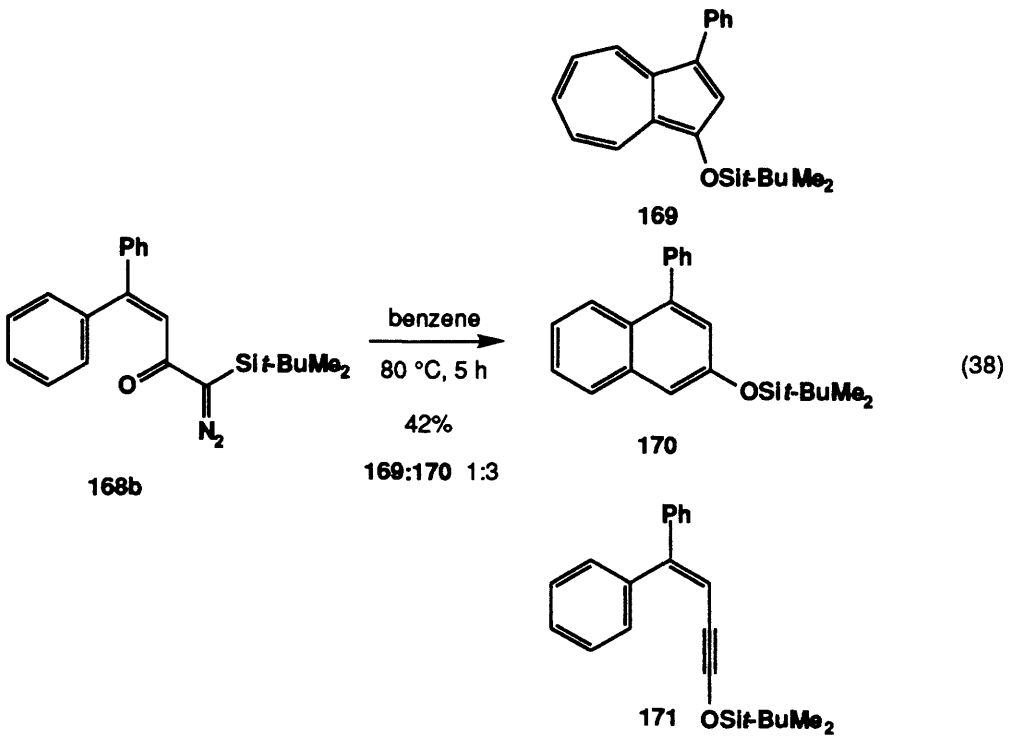
The requisite α-silyldiazo ketones were synthesized using Maas' conditions. Thus, the reaction of diazo enone **93** with various trialkylsilyl triflates gave the expected silylated compounds **168a-c** (eq 37). These compounds were stable at room temperature and could be purified by flash chromatography. The use of purified material in the next step, however, seemed to have little effect on the yield of the subsequent reaction. Thermolysis of **168b** in refluxing benzene did lead to the formation of azulenes in low yields (eq 38).



(37)

93

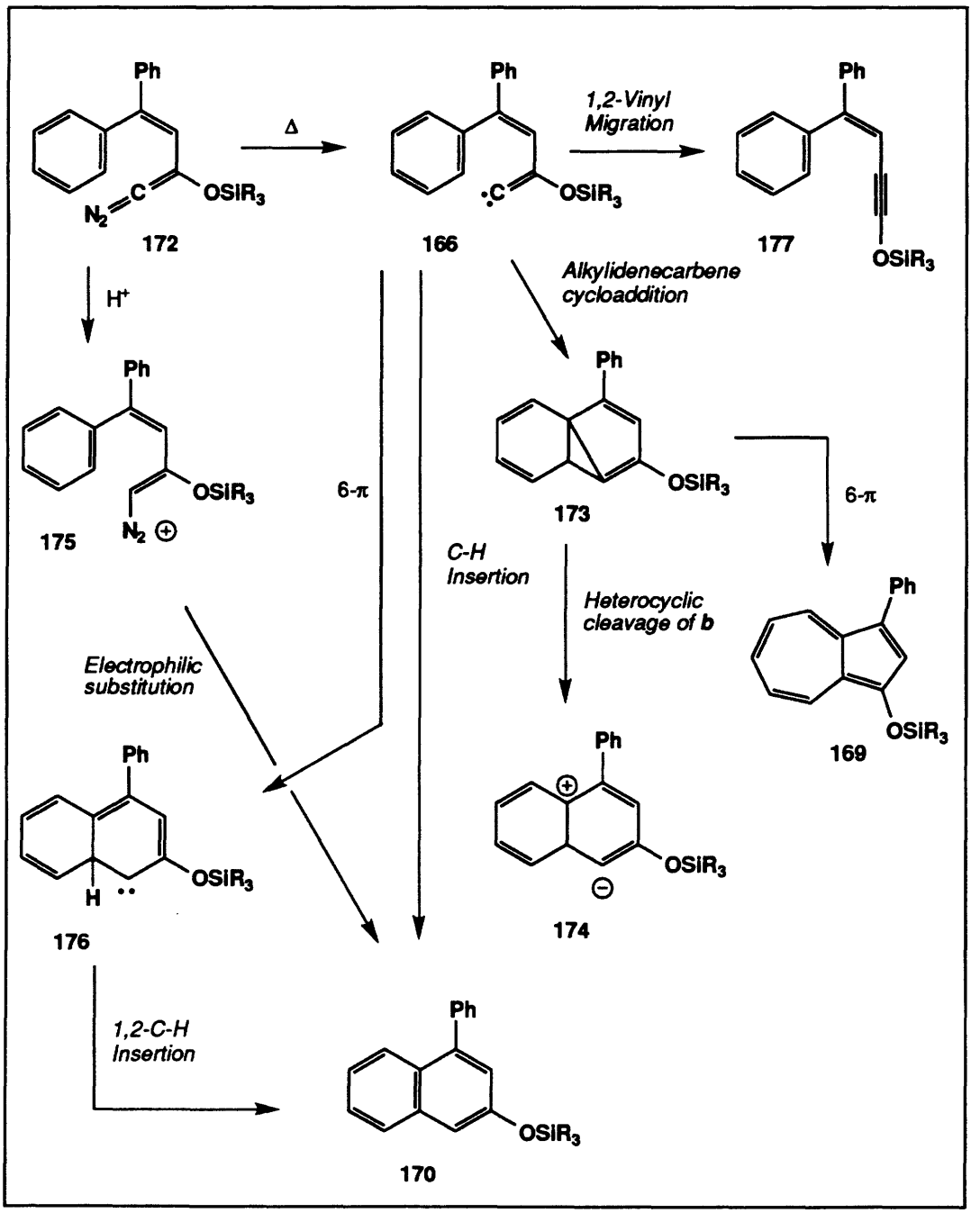
R_3 = *i*-Pr, **168a**
R_3 = *t*-BuMe$_2$, **168b**
R_3 = Me$_2$thexyl, **168c**



(38)

Unfortunately, as in the case of the diazo enone strategy, this reaction was complicated by competing processes. Two major products were isolated from the reaction

Scheme 22



mixture, the desired azulene **169**, and the β-naphthol derivative **170**, with the latter formed preferentially. β-Naphthol **170** can be formed via a number of different processes; outlined in Scheme 22 are several possibilities. Aside from the possibility of heterolytic cleavage of the type seen in the diazo enone strategy, **170** could arise from simple C-H insertion, electrophilic substitution via **175**, or by a combination of 6-π electrocyclic ring closure followed by 1,2-hydrogen migration. IR analysis of the crude reaction mixture also indicated the presence of siloxyacetylene **177**, a result of 1,2-migration of the vinyl substituent. This material, however, could not be isolated because of decomposition during attempted purification.

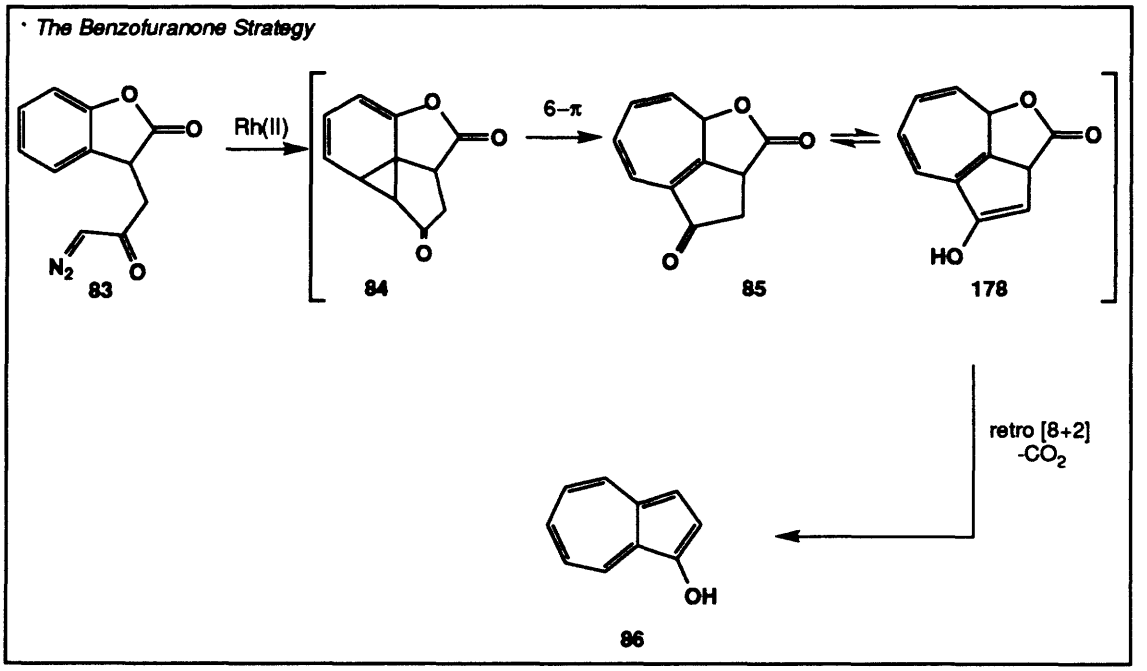
Analysis of the results of these feasibility studies led us to conclude that the alkylidenecarbene strategies were unlikely to provide the basis for an efficient route to substituted azulenes. In particular, it appeared clear that serious side reactions occur in each case studied, and that these competing pathways probably cannot be suppressed. For these reasons, the alkylidenecarbene approaches were abandoned in favor of the new strategies discussed in the following sections.

The Benzofuranone Strategy

The difficulties encountered in the previous strategies can be traced, in large part, to the incorporation of unsaturation in the starting materials. Clearly, new approaches would have to address this problem, perhaps by masking the olefin during the crucial ring expansion-annulation step. One strategy of this type was devised based on the diazo ketone **83**, a benzofuranone derivative (Scheme 23). Treatment of this compound with Rh(II) should lead to an intramolecular Büchner reaction to give tricyclic lactone **85** in which the double bond has isomerized into conjugation with the ketone carbonyl group. Tautomerization to the corresponding enol **178** would set the stage for the unmasking of another C-C double bond via an [8+2] cycloreversion of carbon dioxide; the product 1-

hydroxyazulene (**86**) would then be trapped as before. Note that a similar cycloreversion is involved in the key step in the Nozoe-Takase synthesis of azulenes based on the reaction of cyclohepta[b]furan-2-ones with olefins (see eq 8 in Chapter 1).

Scheme 23



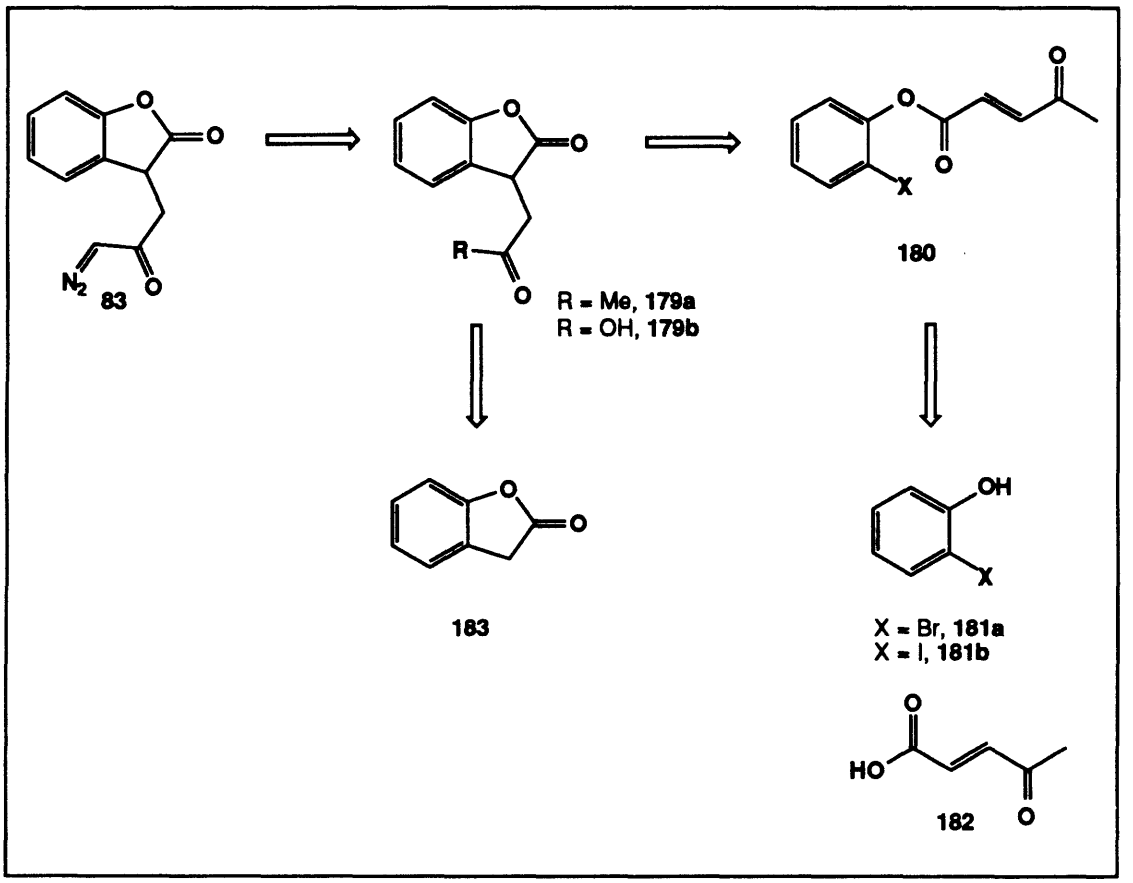
Several routes to diazo ketone **83** appeared possible based on either ketone **179a** or acid **179b** (Scheme 24). At this point; two divergent routes were envisioned to allow access to these compounds. One route was based upon forming the lactone ring via transition metal-promoted or radical-mediated cyclization of *o*-halophenyl ester **180a-b**, which we expected would be readily available from the corresponding phenols **181a-b** and β-acetylacrylic acid (**182**). Another possibility relied upon alkylation of the parent lactone, 2-coumaranone (**183**).

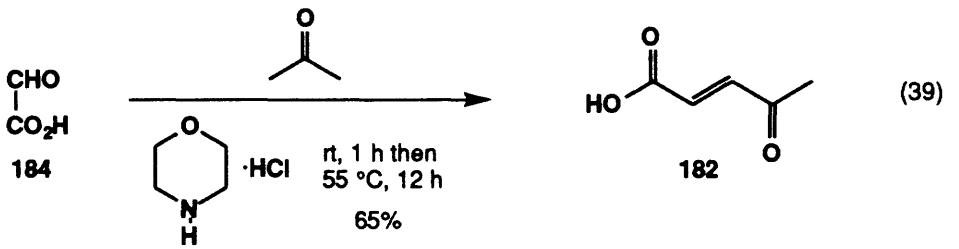
Our initial attempts to form keto lactone **179a** involved the *o*-halophenyl ester approach. β-Acetylacrylic acid (**182**) was produced by the reaction of glyoxylic acid (**184**) with acetone as previously described by Bourguignon (eq 39).[88] While this route

[88]Bourguignon, J. -J.; Schoenfelder, A.; Schmitt, M.; Wermuth, C. -G.; Hechler, V.; Charlier, B.; Maitre, M. *J. Med. Chem.* **1988**, *31*, 893.

does involve a tedious isolation of the desired product via continuous extraction, multigram quantities of the acid are produced in short order.

Scheme 24

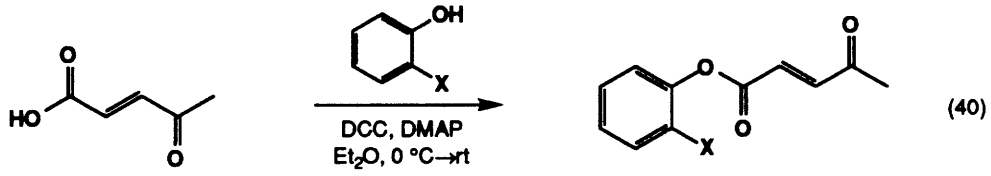




(39)

The esterification of **182** with *o*-halophenols proved to be significantly more difficult than we had first imagined. A variety of esterification methods were employed to

accomplish this transformation, and coupling with 1,3-dicyclohexylcarbodiimide (DCC) provided the best results (eq 40).[89] Other protocols, including methods relying on methanesulfonyl chloride,[90] polyphosphate ester,[91] or chlorotrimethylsilane[92] to activate the carboxylic acid, failed to improve the yield of the desired esters. Surprisingly, the *o*-halophenyl esters proved to be relatively unstable, rapidly decomposing in the presence of nucleophilic species such as excess phenol. These esters also slowly decomposed upon standing in inert solvents. However, the analogous phenyl ester **180c** did not appear to be unstable, leading us to believe that for some reason, possibly electronic or steric in nature, the *o*-halogen atom makes the ester more susceptible to nucleophilic attack.



(40)

Our first choice for ring closure of **180a** and **180b** was via an intramolecular Heck reaction.[93] Various carbocyclic and heterocyclic benzo-fused aromatics have been produced using this strategy. For example, Larock has used this approach to synthesize various oxindoles (eq 41).[94] Treatment of bromide **180a** under Larock's conditions, however, did not lead to the desired lactone; instead, the sole isolated product was 2-bromophenol (**181a**) (eq 42).[95] Varying the reaction conditions by the inclusion of

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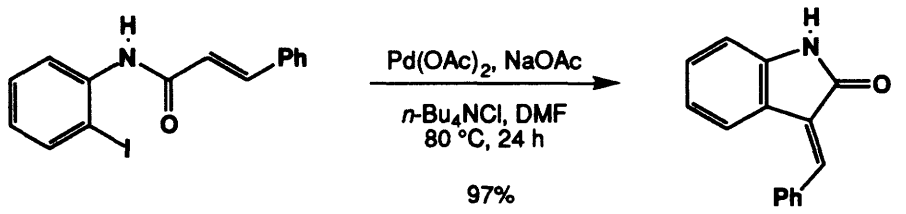
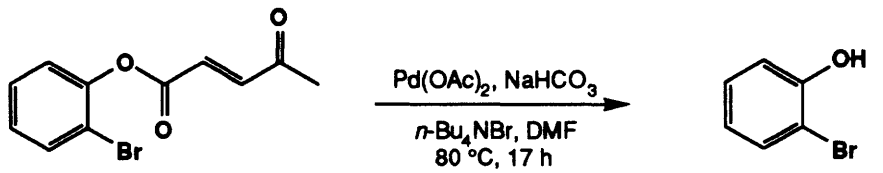
[89]For examples of DCC coupling see: Neises, R.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.
[90]Chandrasekaran, S.; Turner, J. V. *Synth. Commun.* **1982**, *12*, 727.
[91]Adams, J. H.; Lewis, J. R.; Paul, J. G. *Synthesis* **1979**, 429.
[92]Brook, M. A.; Chan, T. H. *Synthesis* **1983**, 201.
[93]For reviews of the Heck reaction see: (a) Heck, R. F. *Palladium Reagents in Organic Syntheses*; Academic Press: London, **1985**. (b) Trost, B. M. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon Press: New York, **1982**; Vol. 8, pp 867-874. (c) Heck, R. F. *Org. Reactions* **1982**, *27*, 345. (d) Daves, G. D.; Hallberg, A. *Chem. Rev.* **1989**, *89*, 1433.
[94]Larock, R. C.; Babu, S. *Tetrahedron Lett.* **1987**, *28*, 5291.
[95]Mori and Ban observed that related substrates also underwent decomposition when treated under Heck conditions. See Mori, M.; Chiba, K.; Ban, Y. *Tetrahedron Lett.* **1977**, 1037.

triphenylphosphine or tetramethylethylenediamine, or increasing the reaction time and/or temperature lead to similar results.



185 186 (41)



180a 181a (42)

A slightly different approach to this cyclization reaction was to form the new ring via a conjugate addition of the corresponding arylcuprate **188**, which we hoped could be formed from the arylzinc halide **187** (Scheme 25). Related intermolecular conjugate additions have recently been reported by Knochel[96] and Rieke.[97] For example, treatment of aryl halide **189** with Zn metal, followed by transmetallation with CuCN·2LiCl gave **190**, which reacted with various organic electrophiles in good to excellent yields (eq 43). In addition, Bronk et al. reported an intramolecular conjugate addition reaction of organozinc halides without the need for transmetallation to the cuprate.[98] This method provides access to various mono- and bicyclic compounds and represents one of the very few successful intramolecular conjugate addition reactions of non-stabilized carbanionic derivatives.

From the outset, application of this type of chemistry to our substrates did not provide encouraging results. Several attempts to form either the arylzinc or the arylcuprate

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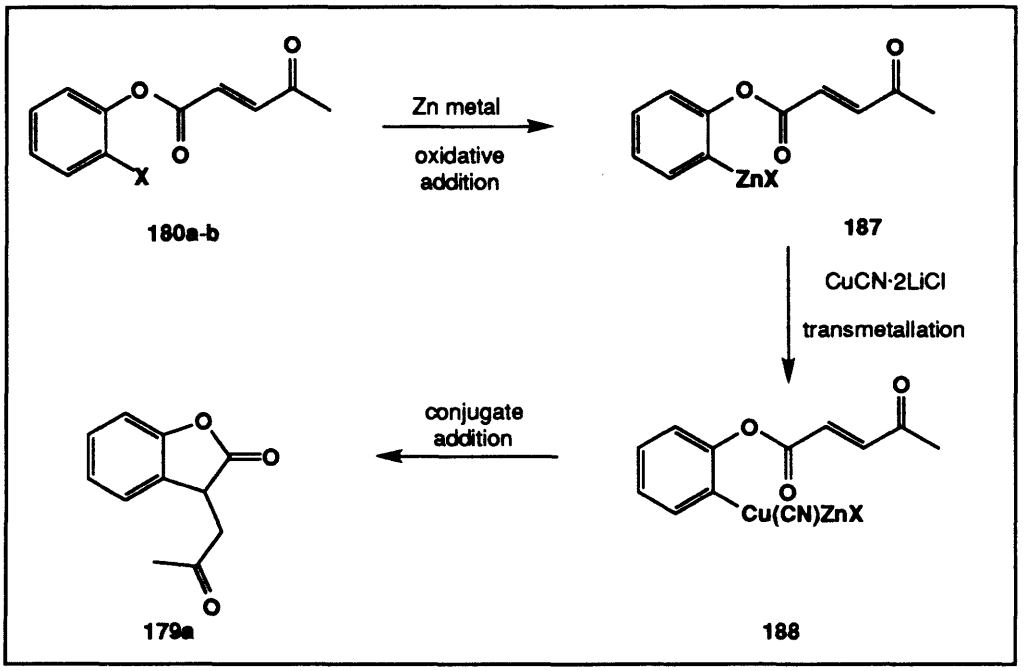
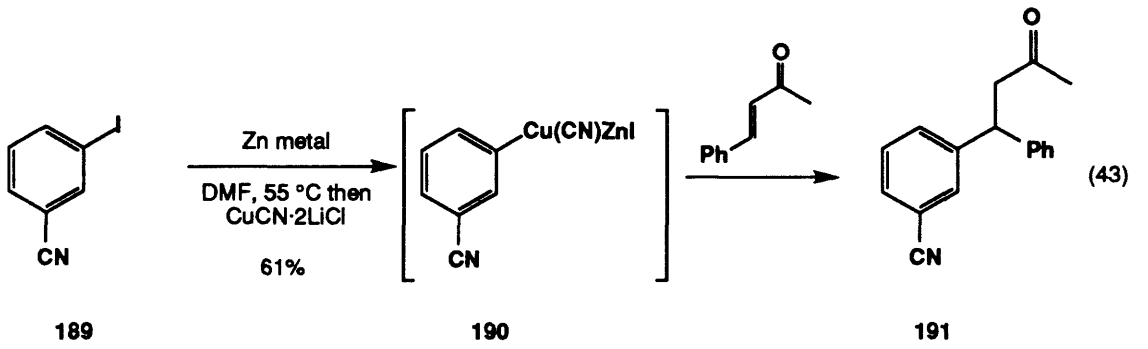
[96]Majid, T. N.; Knochel, P. *Tetrahedron Lett.* **1990**, *31*, 4413.
[97]Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445.
[98]Bronk, B. S.; Lippard, S. J.; Danheiser, R. L. *Organometallics* **1993**, *12*, 3340.

led only to recovered starting material, an indication that the initial oxidative addition of Zn to the C-X bond was not occurring. Further work, while deemed interesting, was suspended pending the outcome of other routes to the lactone.

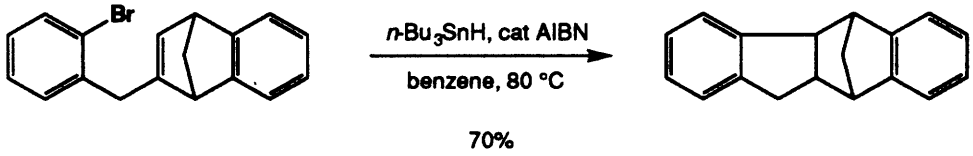
Scheme 25





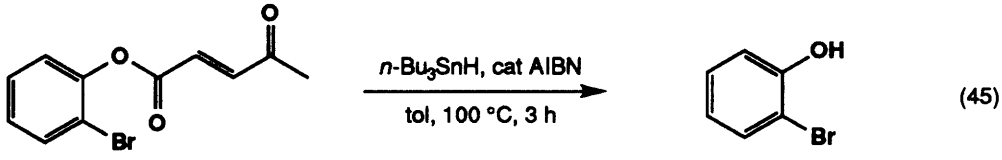
Radical cyclizations have often been employed to carry out transformations similar to those described above. For example, radical cyclizations have been applied extensively

for the construction of various benzo-fused carbocycles and heterocycles.[99] Ghosh and Hart reported the synthesis of the polycyclic aromatic compound **193** via a tri-*n*-butyltin hydride-mediated radical cyclization (eq 44).[100] However, application of these reaction conditions to our substrates (refluxing toluene, catalytic AIBN, slow addition of *n*-Bu_3SnH) led only to the isolation of the cleavage product, 2-bromophenol (**181a**) (eq 45).



(44)

192 **193**



(45)

180a **181a**

While we were not surprised that the ester decomposed under these reaction conditions, we did not expect to isloate **181a** from the reaction mixture. At present, we are unsure why 2-bromophenol is not reduced to phenol by the tin hydride, but this may be an indication of the purity of the *n*-Bu_3SnH used in this reaction. Modifying the reaction conditions by employing freshly prepared tin hydride, increasing or decreasing the rate of addition of *n*-Bu_3SnH, or conducting the reaction with inverse addition (starting material added to *n*-Bu_3SnH) did not alter the outcome. The lack of meaningful progress on these cyclization strategies to the benzofuranone lead us to consider approaching the problem from the other direction. Since we were encountering so many problems forming the lactone ring,

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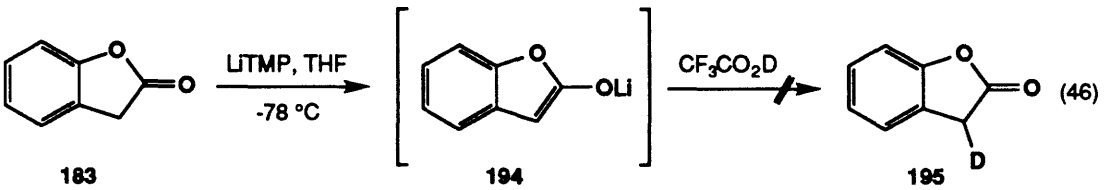
[99]For a review of radical cyclizations, see: Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 4, pp 779-831.
[100]Ghosh, T.; Hart, H. *J. Org. Chem.* **1988**, *53*, 2396.

perhaps it would be wise to start with this ring intact and add the appropriate side chain via alkylation of the lactone enolate.

Benzofuranones via Alkylation Strategies

The alkylation strategies which we envisioned began with the commercially available 2-coumaranone (**183**). We were aware, however, that previous attempts to functionalize the lactone via enolate **194** had met with failure. For instance, Hutchinson had demonstrated that **183** would not undergo deuteration by exposing **194** to deuteriotrifluoroacetic acid; 2-coumaranone was recovered unchanged from the reaction mixture (eq 46).[101] Attempts to carboxylate **183** with methyl methoxymagnesium carbonate were also fruitless.[102]



183 **194** **195**

In 1982, Severin and Lerche reported the alkylation of 2-coumaranone with iodoacetone-*O*-benzyloxime (**196**).[103] Furthermore, the oxime could be converted to the corresponding ketone, the very substrate we desired, by treatment of **197** with aqueous formaldehyde and HCl (eq 47). This revelation seemed to be exactly the answer we were looking for. Unfortunately, we quickly realized that this procedure was not as straightforward as the authors claimed.

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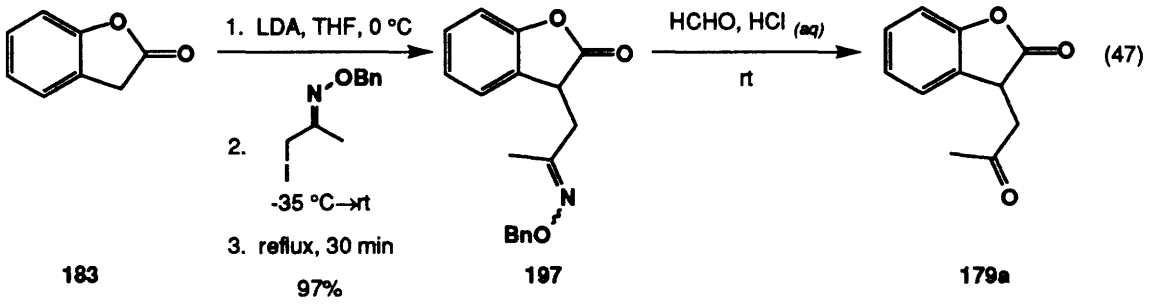
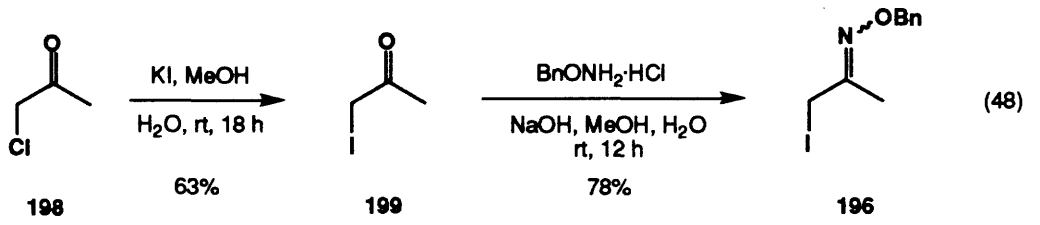
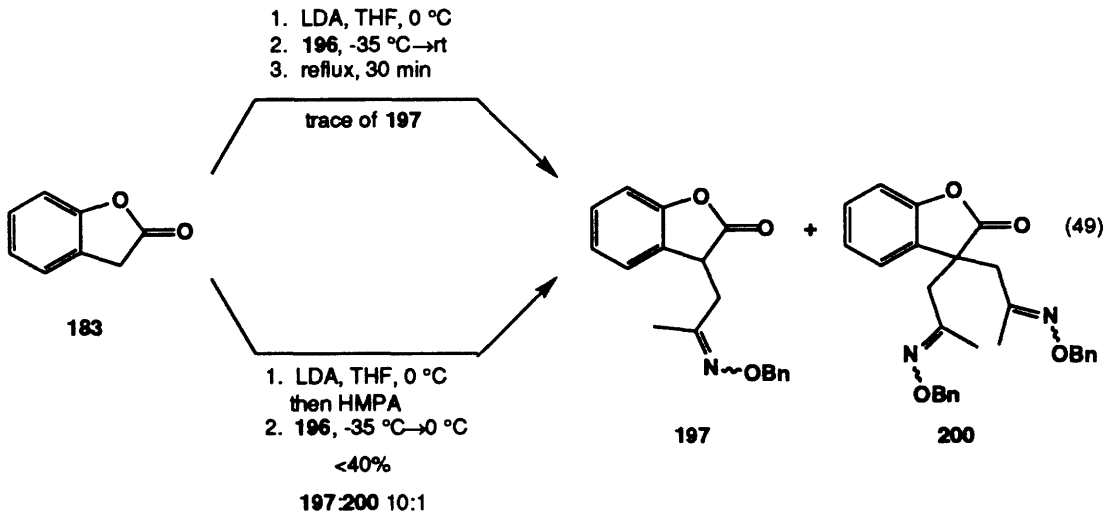
[101]Harmon, A. D.; Hutchinson, C. R. *J. Org. Chem.* **1975**, *40*, 3474.
[102]Martin, J.; Watts, P. C.; Johnson, F. *J. Chem. Soc., Chem. Commun.* **1970**, 27.
[103]Severin, T.; Lerche, H. *Synthesis* **1982**, 305.

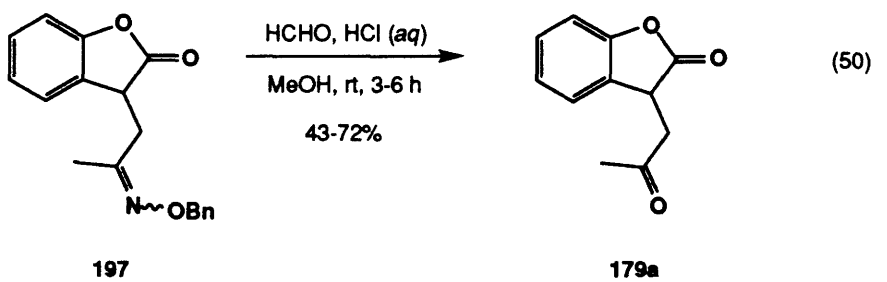


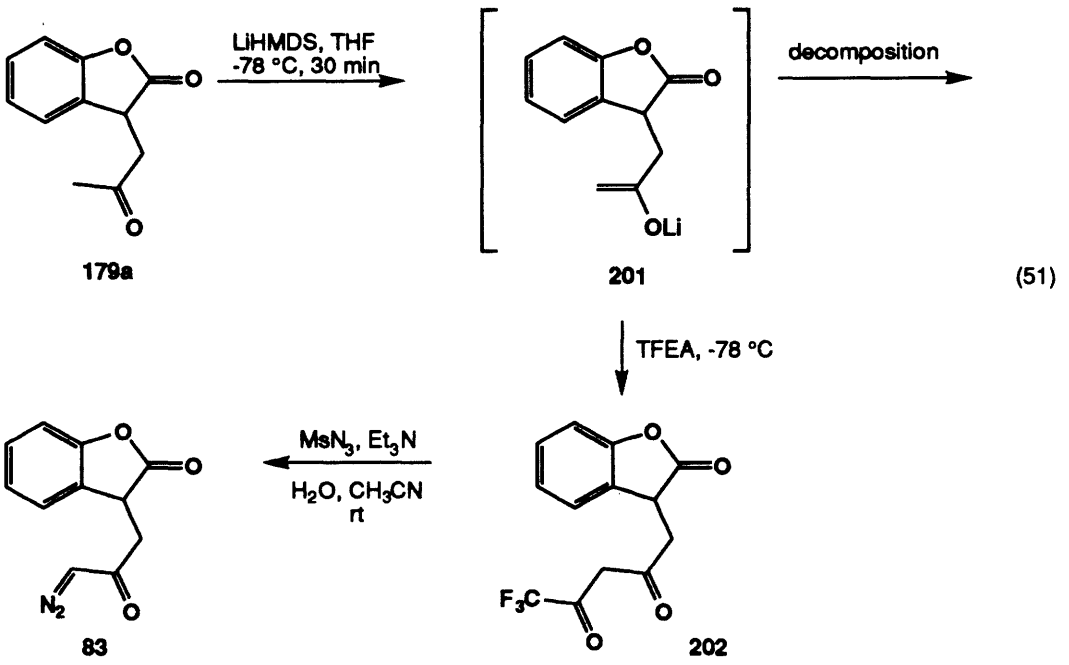
The preparation of the oxime **196** was accomplished as described by Severin and Lerche (eq 48). Starting from chloroacetone (**198**), a Finkelstein reaction provided the iodo derivative **199** which reacted with *O*-benzylhydroxyamine to provide **197** as a mixture of *cis* and *trans* isomers. The reaction of lactone **183** with this reagent under the previously described conditions provided only a trace of the desired product. By eliminating the reflux step and quenching the reaction at 0 °C, **197** was obtained in 26% yield (eq 49). Also isolated from this reaction was a compound which appeared to be the dialkylated product **200**. Yields were not improved by forming the enolate with LiHMDS or by the addition of cosolvents such as HMPA.





While we were disappointed not to be able to repeat the literature results, a considerable amount of lactone **197** had been produced during our attempts. The conversion of this material to keto lactone **179a** was accomplished in good yield (eq 50). Imagine our dismay, then, when treatment of this material under our diazo group transfer procedure led exclusively to decomposition of the starting material (eq 51). No identifiable organic compounds were isolated from the reaction residue. In hindsight, the decomposition of **179a** under basic conditions is not surprising, presumably occurring through intramolecular attack on the lactone by the ketone enolate. We did, however, take comfort is the fact that very reactive electrophiles would alkylate, at least to a certain extent, enolate **194**. By incorporating another diazo ketone precursor, such as a carboxylic acid, into the lactone system, this strategy might still be useful.





In fact, as shown in Scheme 26, the reaction of **183** with *t*-butyl iodoacetate (**203**) provided lactone **204** in moderate yield. Cleavage of this ester to give acid **179b** could be accomplished with either trifluoroacetic acid or chlorotrimethylsilane/sodium iodide. In the presence of acid, however, a mixture of the γ- and δ-lactones is formed, making the latter approach superior. The Arndt-Eistert protocol is the classical method for the synthesis of diazo ketones from carboxylic acids.[104] This two step process involves the conversion of the acid to the corresponding acyl chloride followed by quenching with diazomethane. Application of this method to our substrate provided encouraging results; IR analysis of the crude reaction product indicated the presence of both a diazo ketone and lactone moiety (eq 52). Attempted purification of this material by flash chromatography, however, lead to its complete destruction. Although we were unable to isolate a purified product from this reaction, we were encouraged by our initial results. By simply repeating the final step of this sequence and careful purification of the diazo compound, the ring expansion/annulation substrate could be produced.

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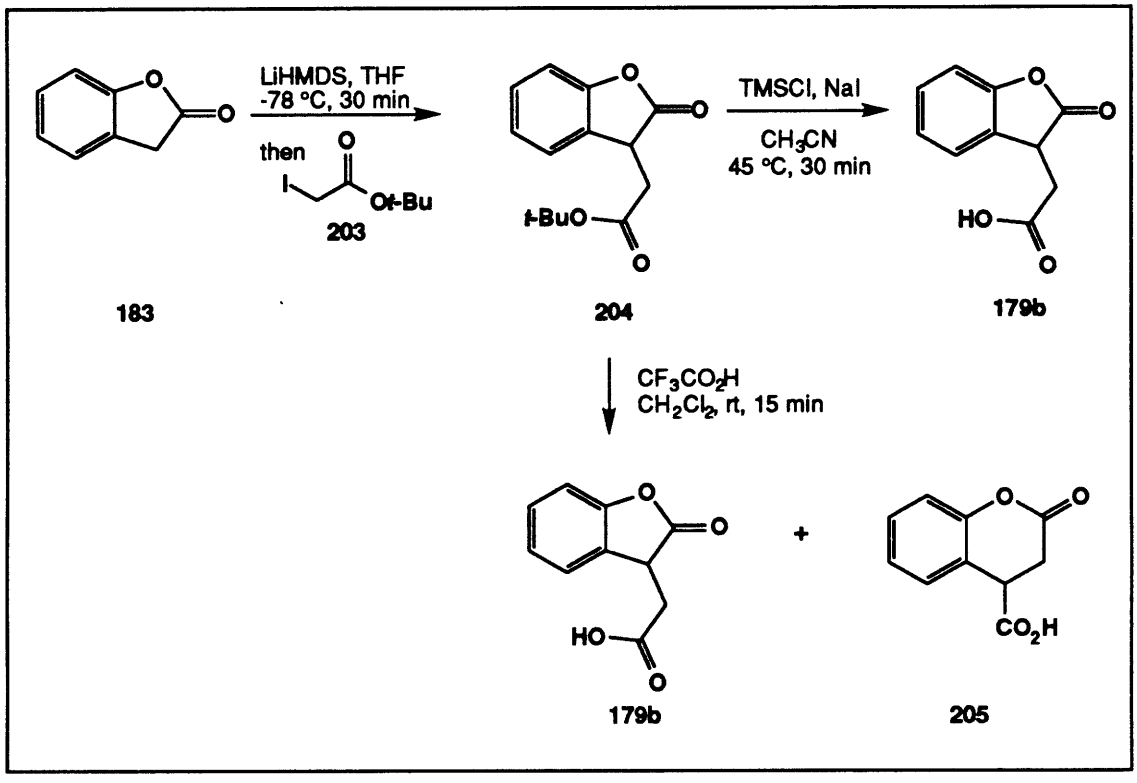
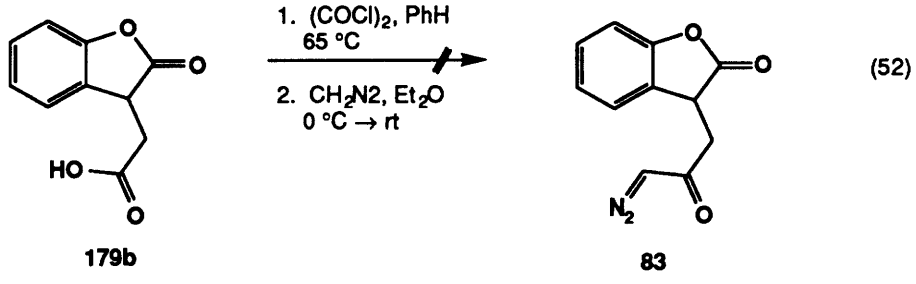
[104](a) Arndt, F.; Eistert, B.; Partale, W. *Chem. Ber.* **1927**, *60*, 1364. (b) Arndt, F.; Amend, J. *Chem. Ber.* **1928**, *61*, 1122. (c) Arndt, F.; Eistert, B. *Chem. Ber.* **1935**, *68*, 200. (d) Reviewed in Bachmann, W. E.; Struve, W. S. *Org. React.* **1942**, *1*, 38.

Scheme 26





(52)

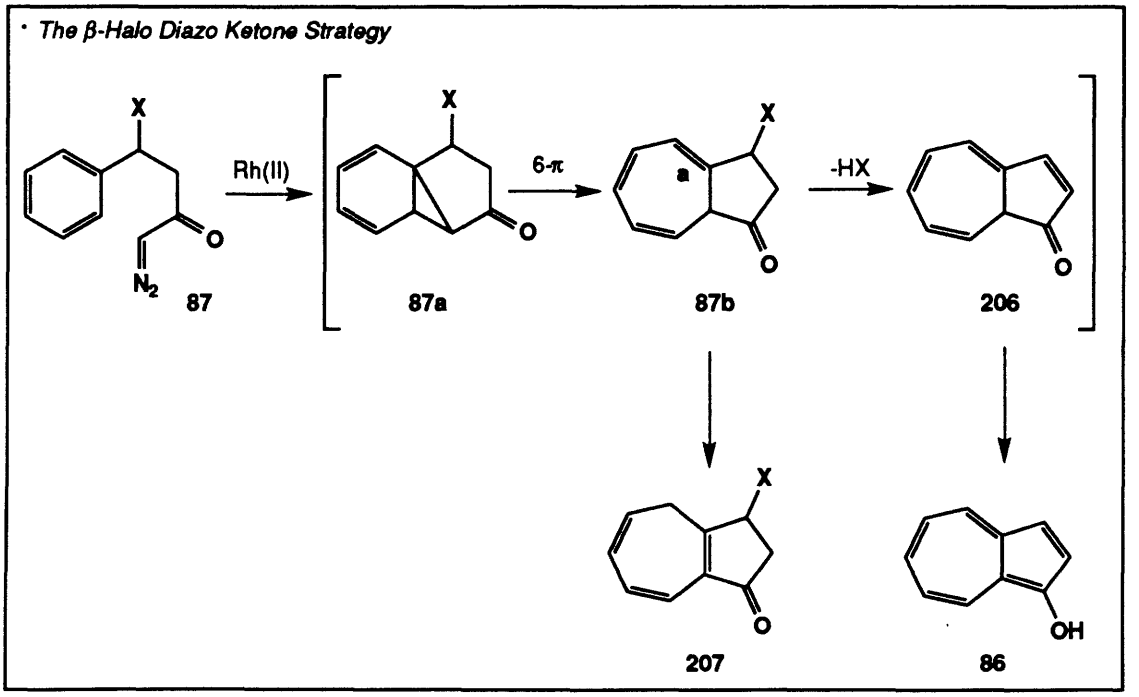
In spite of the promise we thought this route held, a new strategy had begun to show even more encouraging results. As this alternative route to azulenes became more attractive, less attention was focused on the benzofuranone approach, and the final step mentioned above was never repeated. Instead, the new "β-halo diazo ketone strategy" became the focus of our research efforts. Details of this successful approach are presented in the following chapter.

CHAPTER 3

Ring Expansion-Annulation Approaches to Substituted Azulenes
Part II: The β-Halo Diazo Ketone Strategy

Our final and successful approach to substituted azulenes is based on the Büchner reaction of diazo ketones with a leaving group in the β-position to the carbonyl group. As outlined in Scheme 27, it was thought that treatment of a suitably substituted diazo ketone **87** under the standard intramolecular Büchner reaction conditions would lead to hydroazulenone **87b** via 6-π electrocyclic ring opening of the norcaradienone intermediate **87a**. The addition of a base would then cause **87b** to undergo either an elimination of HX or the type of alkene isomerization reaction (**87b** → **207**) seen previously in the work of Scott and McKervey. Ideally, the elimination of HX would occur faster, leading to 1-hydroxyazulenes via enone **206**.

Scheme 27



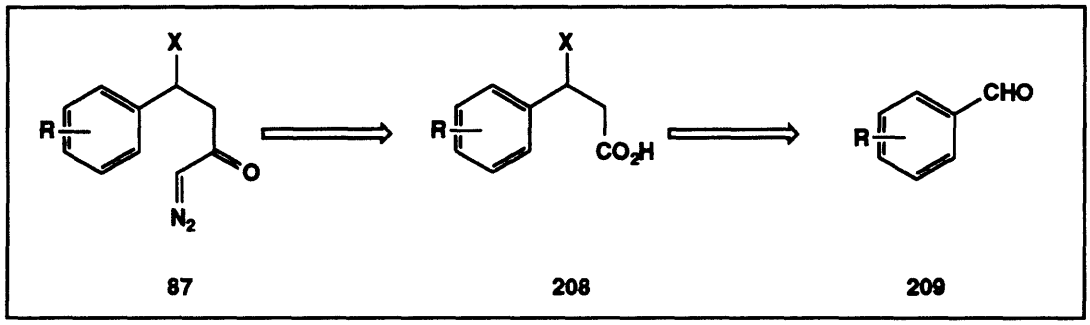
If, on the other hand, olefin isomerization were the faster reaction, then it might be possible that this process could be reversible, and the desired conversion to **86** might still be possible. It appeared likely that the nature of the β-leaving group would be an important factor in determining the outcome of this step of the process. We believed that by judicious choice of leaving group, the reaction would proceed to give azulenes.

Substrate Synthesis

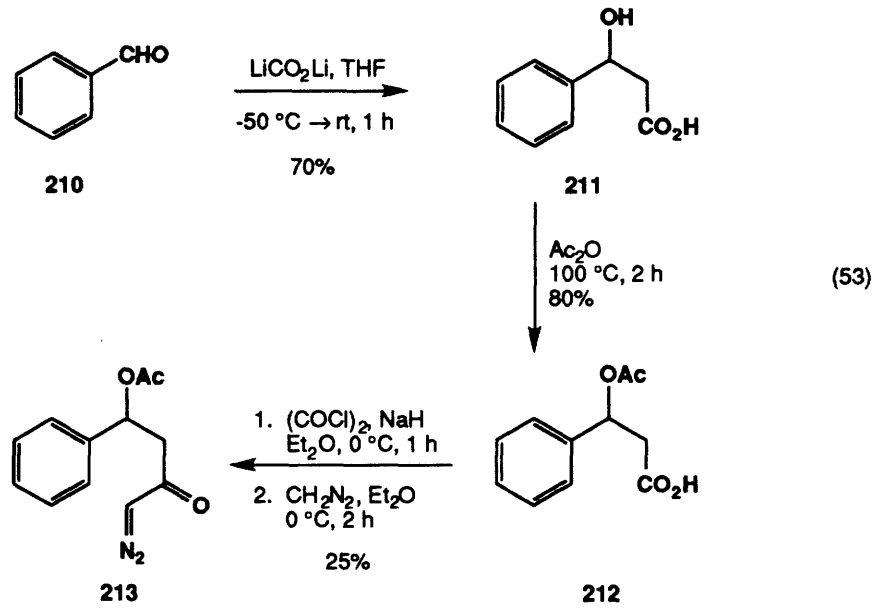
Several considerations guided our efforts in developing routes to the various substrates we required for this new ring expansion-annulation reaction. One of our foremost concerns was the availability of starting materials. In order to demonstrate a significant advance over existing azulene forming reactions, we believed that access to a variety of β-substituted diazo ketones (with variations in both type and position of substituent) was necessary. We therefore focused our efforts on routes that would employ readily available aromatic compounds as starting materials, and which would involve conditions compatible with a wide range of functionality on the aryl ring.

Scheme 28 outlines our basic strategy for the synthesis of ring expansion-annulation substrates. The diazo ketone **87** was envisioned as arising from 3-phenylpropionic acid derivatives **208** via the Arndt-Eistert protocol. Starting from the corresponding benzaldehyde derivatives, various one- and two-step sequences to provide **208** and allow us to vary the β-leaving group seemed feasible. The choice of benzaldehyde derivatives as starting materials appeared to be logical since a large number of these compounds are commercially available at low cost and with a variety of substitution patterns.

Scheme 28



Our original plans called for examination both halogen and oxygen leaving groups at the β-position. One of our earliest target substrates was the acetoxy derivative **213** which was prepared as outlined in eq 53. The reaction of benzaldehyde with the dianion of acetic acid according to the procedure of Mulzer gave the known hydroxy acid **211** in good yield.[105]



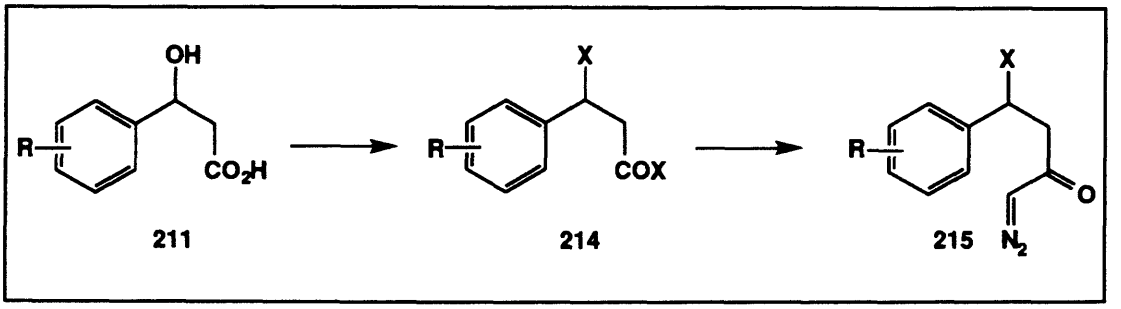
(53)

[105]Mulzer, J.; Segner, J.; Brüntrup, G. *Tetrahedron Lett.* **1977**, 4651.

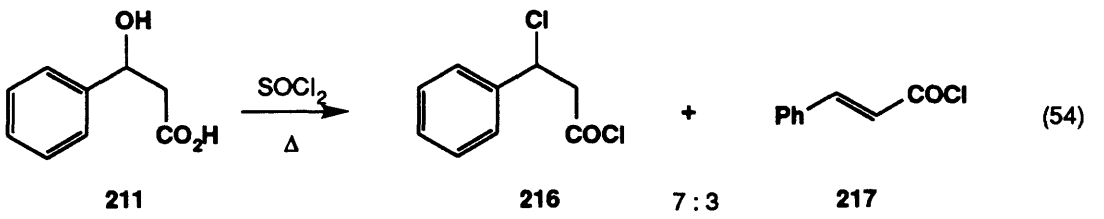
Conversion of this material to our first annulation substrate was accomplished by acetylation of the alcohol with acetic anhydride to give β-acetoxy acid **212**,[106] followed by acid chloride formation and reaction with diazomethane to give the diazo ketone **213**. Although the yield for converting **211** to **213** was rather low, we were confident that the yield of this sequence could be improved if warranted.

It occurred to us that hydroxy acid **211** might also be useful for the preparation of the corresponding β-halo derivatives. As illustrated in Scheme 29, we envisioned a two-step process to transform **211** to a β-halo diazo ketone: conversion the benzylic alcohol to a halide while simultaneously forming the acyl halide, followed by quenching with diazomethane. Our initial experiments were primarily focused on determining conditions for converting hydroxy acid **211** to the β-halo acyl halide **214**. The reaction of **211** with neat thionyl chloride at elevated temperatures (eq 54) led to the formation of the desired β-chloro acid chloride **216**; however, under these conditions, a significant amount of cinnamoyl chloride (**217**) was also formed. While this initial result appeared promising, milder conditions appeared necessary in order to prevent the formation of **216** via elimination of HCl. Thus, an extensive study of various halogenating reagents was undertaken.[107]

Scheme 29



[106]La Mer, V. K.; Greenspan, J. *J. Am. Chem. Soc.* **1934**, *56*, 1492.
[107]For an overview of the methods available for the coversion of alcohols to halides and carboxylic acids to acyl halides, see: Larock, R. C. *Comprehensive Organic Transformations*; VCH Publishers; New York, 1989: pp 353-360 and pp 963-964.



Some of the results of this study are summarized below in Table 3. Reactions involving thionyl chloride as the chlorinating reagent gave significant amounts of the elimination product, even when conducted in solution at room temperature with catalytic N,N-dimethylformamide (entries 1-3).[108,109] Under milder conditions using reagents such as carbon tetrachloride/triphenylphosphine (entry 4)[110] or oxalyl chloride/dimethylsulfoxide (entry 5),[111] the amount of desired product formed was even lower than with thionyl chloride. Our best results came by employing two phosphorous-based reagents. Treatment of **211** with neat phosphorous pentachloride gave an 6:1 ratio of the desired β-chloro acid chloride to cinnamoyl chloride (entry 6); however, further increases in the yield of **216** could not be realized with this system. While these reagents were unable to provide **216** without the concomitant formation of **217**, triphenylphosphine dibromide[112] furnished the analogous β-bromo acyl bromide free from any of the corresponding α,β-unsaturated acyl bromide (entry 7). We were concerned, however, that the less stable acid bromides would be more difficult to handle, and thus we began searching for alternative methods of synthesizing these β-halo acyl halides.

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[108]Floyd and Allen reported the use of the $SOCl_2$/DMF system in their conversion of β-hydroxy acids to β-chloro acid chlorides; however, they make no mention of any competing HCl elimination. See Floyd, M. B.; Allen, G. R., Jr. *J. Org Chem.* **1970**, *35*, 2647.

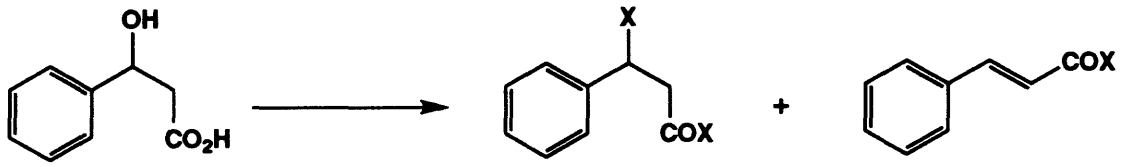
[109]Bosshard, H. H.; Mory, R.; Schmid, M.; Zollinger, H. *Helv. Chim. Acta* **1959**, *42*, 1653.

[110](a) Lee, J. B. *J. Am. Chem. Soc.* **1966**, *88*, 3440. (b) Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801. For a related procedure see: (c) Harrison, C. R.; Hodge, P.; Hunt, B. J.; Khoshdel, E.; Richardson, G. *J. Org. Chem.* **1983**, *48*, 3721.

[111]For examples see: (a) Kende, A. S.; Johnson, S.; Sanfilippo, P.; Hodges, J. C.; Jungheim, L. N. *J. Am. Chem. Soc.* **1986**, *108*, 3513. (b) Kato, N.; Nakanishi, K.; Takeshita, H. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1109.

[112](a) Aizpurua, J. M.; Palomo, C. *Synthesis* **1982**, 684. (b) Aizpurua, J. M.; Cossio, F. P.; Palomo, C. *J. Org. Chem.* **1986**, *51*, 4941.

Table 3



211

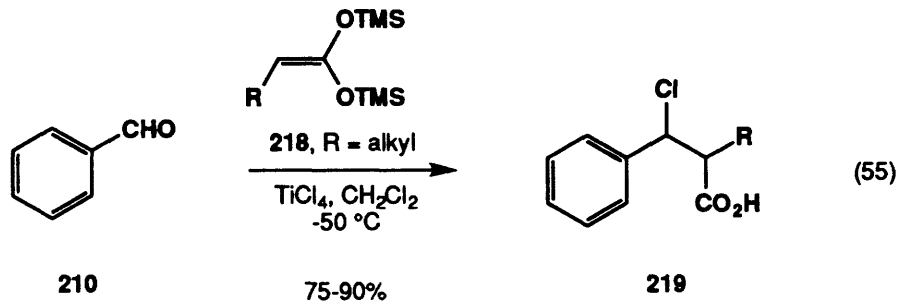
X = Cl, **216a**
X = Br, **216b**

X = Cl, **217a**
X = Br, **217b**

entry	reagents	conditions	product ratios	
			dihalide **216a-b**	elimination product
1	11 equiv $SOCl_2$	80 °C, 1h	70	30
2	5.6 equiv $SOCl_2$, cat. DMF, tol	rt, 6 h	72	27
3	5.6 equiv $SOCl_2$, cat. DMF, tol	70 °C, 6 h; rt, 16 h	71	29
4	2.0 equiv Ph_3P, CCl_4, CH_3CN	80 °C, 9.5 h; rt, 13 h	0	trace
5	2.4 equiv $(COCl)_2$, DMSO	-60 °C to rt, 3h	0	0
6	2.0 equiv PCl_5	rt, 2 h	85	14
7	2.0 equiv Ph_3PBr_2, CH_2Cl_2	rt, 45 min	100	0

In 1988, Bellassoued and coworkers reported a one step route to β-chloro acids via a Mukaiyama-type aldol reaction involving various bis(silylketene) acetals and benzaldehyde (eq 55).[113] This reaction works particularly well for cases where substituted bis(silylketene) acetals are employed (i.e. R ≠ H), providing the desired chloro acids in 75-90% yield. However, no mention was made in this report of reactions which employed the bis(silylketene) acetal of acetic acid (i.e. R = H). Therefore, a study to determine the feasibility of this variant of the Mukaiyama aldol process as applied to this substrate was undertaken.

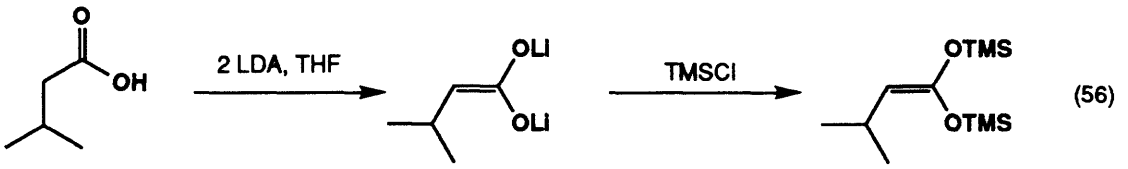
[113]Bellassoued, M.; Dubois, J. -E.; Bertounesque, E. *Tetrahedron Lett.* **1988**, *29*, 1275.



(55)

210 75-90% 219

The bis(silylketene) acetal of acetic acid is not as easily produced or handled as are homologous substituted systems. In the case of substituted derivatives, reaction of the dilithio anion of the carboxylic acid with chlorotrimethylsilane provides the desired ketene acetal in good yield (e.g., eq 56).[114] However, as shown in Scheme 30, treatment of acetic acid under these conditions leads to a moderate yield of the desired product **224**; significant amounts of the *C*-silylated compound **225** are also produced.[115] The desired bis(silylketene) acetal **224** can be produced in high yield by a modification of the original reaction conditions. Bellassoued and Gaudemar found that the *sodium* enolate of trimethylsilyl acetate reacts preferentially at oxygen to give the acetal.[115] Using this procedure, we were able to synthesize **224** for study in the Mukaiyama reaction. This acetal, however, is rather susceptible to hydrolysis, thus requiring that the compound be freshly prepared before each Mukaiyama aldol reaction.



(56)

220 221 222

We found that the reaction of **224** with benzaldehyde does lead to the formation of the desired β-chloro acid, albeit in low yield (eq 57). Whether this low yield is a function of the purity of **224** or its stability under the reaction conditions is unknown.

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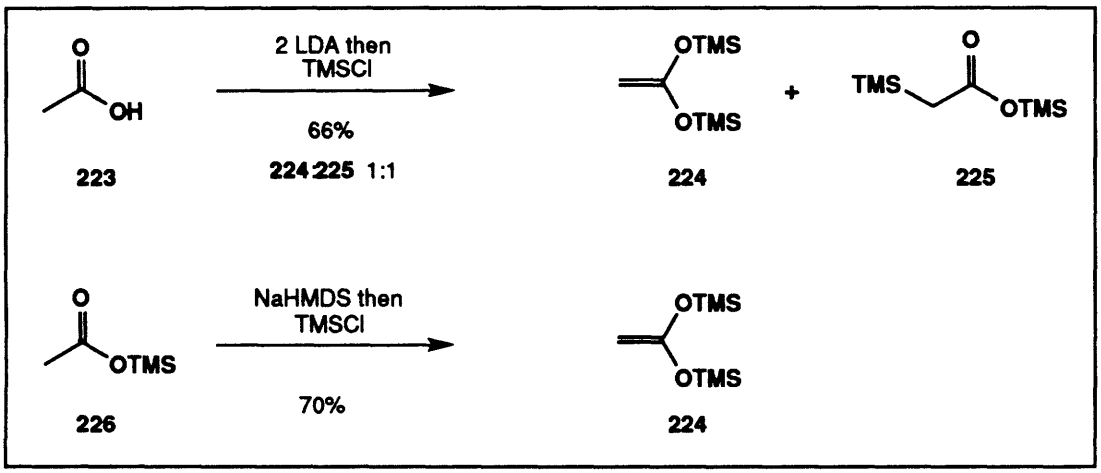
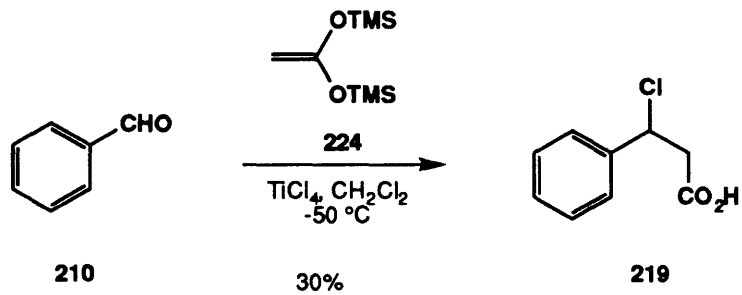
[114]Ainsworth, C.; Kuo, Y. -N. *J. Organomet. Chem.* **1973**, *46*, 73.
[115]Bellassoued, M.; Gaudemar, M. *Tetrahderon Lett.* **1990**, *31*, 209.

Scheme 30



Considering the difficulties encountered in handling this reagent and the low yield of the aldol step, we concluded that this approach to β-chloro acids has only limited appeal.



(57)

While the Mukaiyama route appeared to be of little value for preparing the β-chloro acid we desired, hydrohalogenation of the olefin of cinnamic acid derivatives seemed to offer an attractive alternative (Scheme 31).[116] The choice of cinnamic acids as substrates appeared to be a good one, given that a number of these acids are commercially available or easily prepared in one step from benzaldehyde derivatives.[117] Our initial attempts to add

[116]For reviews of hydrohalogenation reactions of alkenes and alkynes, see: (a) Larock, R. C.; Leong, W. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 4, pp 269-321. (b) Stacey, F. W.; Harris, J. F., Jr. *Org. Reactions* **1963**, *13*, 150. (c) Parker, R. E.; Issacs, N. S. *Chem. Rev.* **1959**, *59*, 737.

[117]Numerous examples of cinnamic acid syntheses from benzaldehydes via the Knoevenegal reaction are presented in Jones, G. *Org. Reactions* **1967**, *15*, 204.

both HCl and HBr to cinnamic acid, however, indicated that this process was more difficult than first anticipated (Table 4). Attempted hydrochlorination of **227** with anhydrous HCl in diethyl ether led to complete recovery of starting material (entries 1-2). As expected, the addition of anhydrous HBr occurred much more readily, but this reaction was complicated by the formation of the corresponding ethyl ester on extended reaction times (entries 3-4). Presumably, under these conditions some of the diethyl ether is cleaved by HBr to generate ethyl bromide and ethanol, both of which would be capable of esterifying **228**. Unfortunately, changing to halogenated or aromatic solvents decreased the efficiency of the hydrobromination reaction, providing a mixture of the desired product and starting material (entries 5-7). The incomplete reaction in dichloromethane may be due to a complex solubility problem involving the alkene **227**, HBr, and the solvent. As the reaction mixture is treated with anhydrous HBr, cinnamic acid precipitates from the solution, creating two phases. This biphasic system may account for the longer reaction times and the incomplete conversion of **227** to the desired product. This solubility problem can be minimized by performing the reaction at more dilute concentrations, but this becomes an unattractive alternative as the reaction is scaled up.

Scheme 31

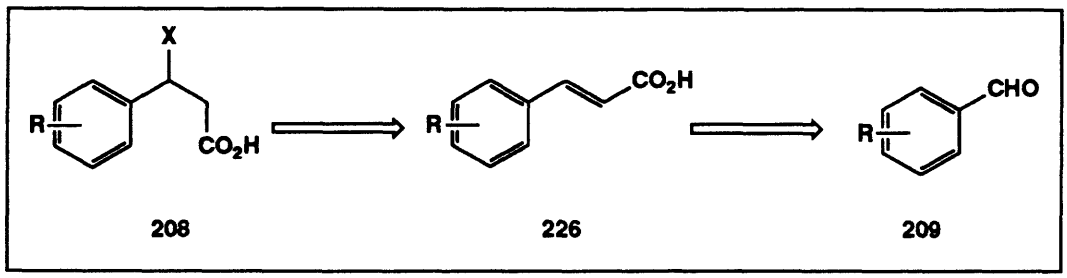
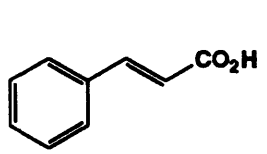
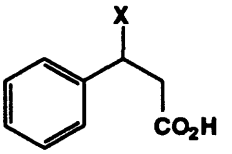


Table 4



227



228

entry	HX	conditions	ratio 228:227
1	HCl	Et_2O, rt, 1 h	no reaction
2	HCl	Et_2O, rt, 19 h	no reaction
3	HBr	Et_2O, rt, 4 h	87 : 13
4	HBr	Et_2O, rt, 20 h	ethyl ester of **228**
5	HBr	CH_2Cl_2, rt, 23 h	81 : 19
6	HBr	$Cl(CH_2)_2Cl$, -20 °C to rt, 80h	67 : 33
7	HBr	PhH, rt, 19 h	no reaction

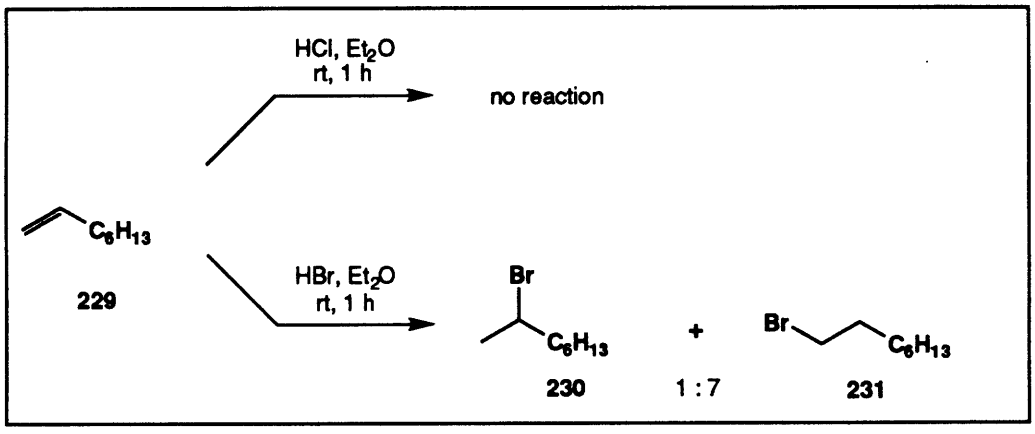
The difficulties which plagued the addition of HX to cinnamic acid have also complicated the hydrohalogenation of simple alkenes and alkynes. For example, Kropp and coworkers reported that no reaction takes place upon treatment of 1-octene (**229**) with anhydrous HCl in diethyl ether (Scheme 32). The reaction of **229** with HBr did occur; however, the undesired anti-Markovnikov addition product **231** (resulting from a radical chain process) was the major product, while the desired bromide **230** was produced only in small amounts. These researchers found, however, that the hydrohalogenation of alkenes and alkynes becomes a reliable synthetic transformation if the reaction is conducted in the presence of a suitable "surface agent", such as activated alumina or silica gel.[118,119] It appears that Al_2O_3 and SiO_2 reduce entropy effects by bringing the reactants together on

[118](a) Kropp, P. J.; Daus, K. A.; Crawford, S. D.; Tubergen, M. W.; Kepler, K. D.; Craig, S. L.; Wilson, V. P. *J. Am. Chem. Soc.* **1990**, *112*, 7433. (b) Kropp, P. J.; Daus, K. A.; Tubergen, M. W.; Kepler, K. D.; Wilson, V. P.; Craig, S. L.; Baillargeon, M. M.; Breton, G. W. *J. Am. Chem. Soc.* **1993**, *115*, 3071.

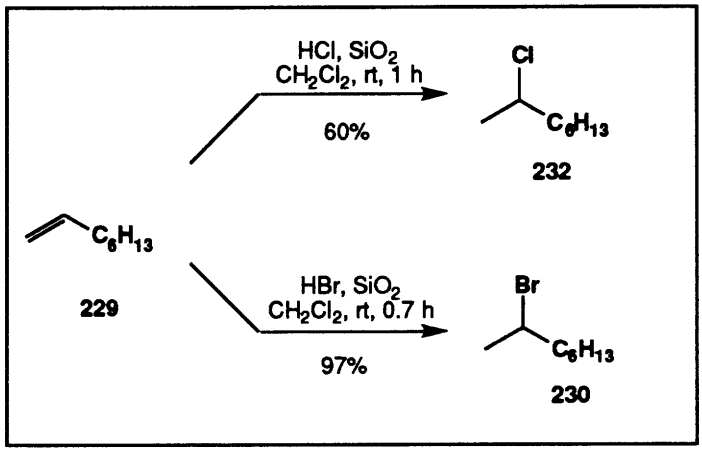
[119]The surface agents are activated by drying at 120 °C for at least 48 h.

their surfaces, thus increasing the rate of HX addition. Furthermore, these surface agents promote ionic addition to olefins, thus eliminating competitive radical addition processes. The treatment of 1-octene with HCl or HBr in the presence of either alumina or silica gel leads to synthetically useful yields of both the desired chloride **232** and bromide **230** (Scheme 33). This procedure is also successful when HX precursors such as $(COX)_2$ or SOX_2 are employed in place of gaseous HX.

Scheme 32



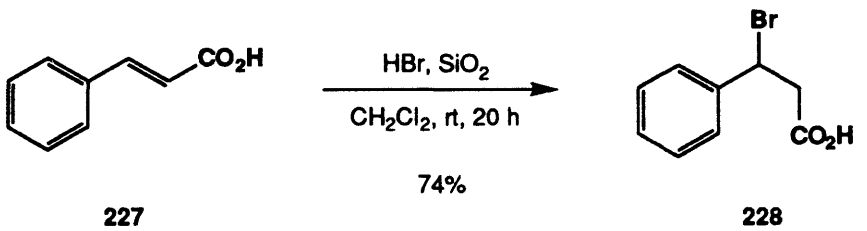
Scheme 33



To our knowledge, Kropp's procedure has not previously been applied to substrates other than simple alkenes and alkynes. It was unknown whether this protocol would be effective for the addition of HX to functionalized olefins such as our cinnamic

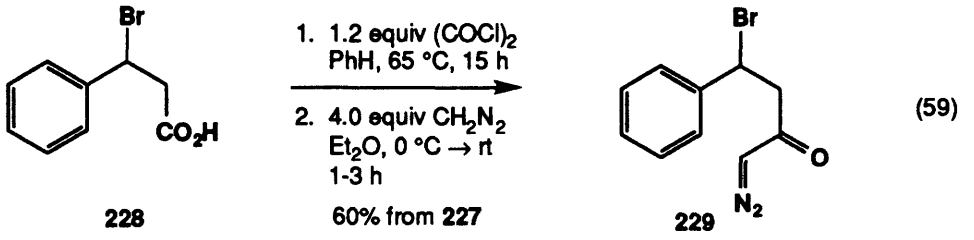
acids. We quickly found, however, that this method was indeed capable of promoting the hydrobromination of cinnamic acid (eq 58): complete conversion of **227** to 3-bromo-3-phenylpropionic acid (**228**) was observed upon treatment of a mixutre of **227** and silica gel (10 g per gram of substrate) in dichloromethane with excess HBr. After 20 h at room temperature, filtration of the solid support and concentration of the filtrate provided crude **228**. Recrystallization of this material from cyclohexane provided **228** as a white solid (mp 92-94 °C) with spectral charateristics identical to those reported by McGarvey and Knipe.[120] This material could be stored under an inert atmosphere for several weeks without significant decomposition. The hydrobromination of **227** was also promoted by alumina, but the reaction appeared to be slower.

Chapman had previously demonstrated that the β-bromo acid **228** could be converted to the corresponding diazo ketone **229** by treatment with oxalyl chloride and diazomethane.[121] Indeed, application of this Arndt-Eistert protocol to **228** provided **229** in 60% yield for the three steps from cinnamic acid (eq 59). Unfortunately, hydrochlorination of **227** with anhydrous HCl or with HCl precursors (such as oxalyl chloride or thionyl chloride) under the same conditions employed for the HBr addition did not prove feasible; in each cae, unreacted alkene was recovered unchanged.



227 228 (58)

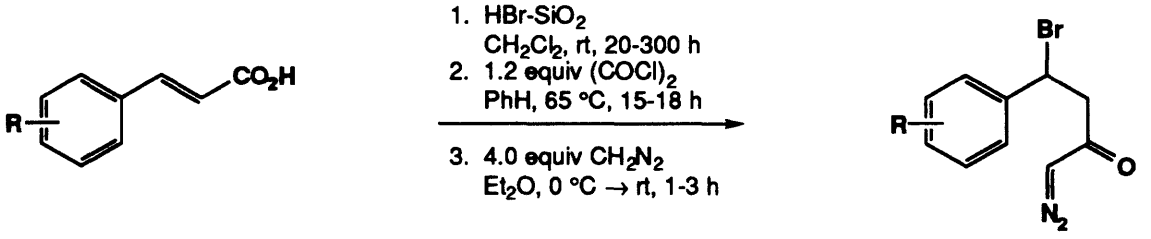
[120]McGarvey, J. E. B.; Knipe, A. C. *J. Chem. Ed.* **1980**, *57*, 155.
[121]Rosenquist, N. R.; Chapman, O. L. *J. Org. Chem.* **1976**, *41*, 3326.



228 229 (59)

With the discovery that this simple three step process could produce the desired β-bromo diazo ketones, we next examined its application to a variety of substituted cinnamic acid derivatives (Table 5).

Table 5



entry	cinnamic acid	diazo ketone	% yield
1	**227** (R = H)	**229**	60
2	**233** (R = 2-Cl)	**234**	51
3	**235** (R = 2-I)	**236**	51
4	**237** (R = 3-*i*-Pr)	**233**	51-60
5	**239** (R = 3-Br)	**240**	55
6	**241** (R = 3-CF_3)	**242**	30
7	**243** (R = 4-Me)	**244**	47
8	**245** (R = 4-Cl)	**246**	51
9	**247** (R = 3,4-di Cl)	**248**	45

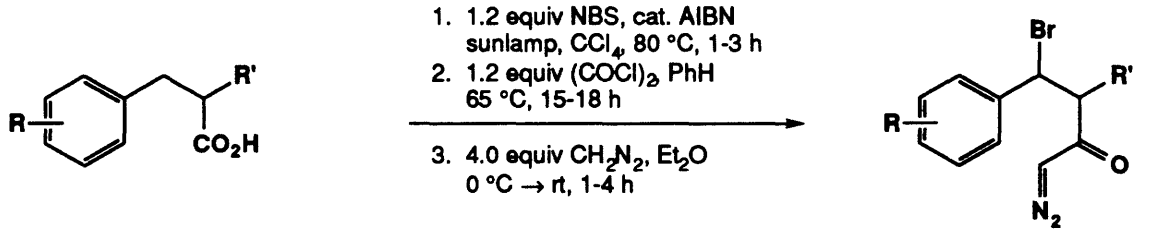
The nature of the substituent on the aromatic ring had a direct influence on the outcome of the HBr addition step. For cinnamic acids which incorporate an electron-donating group, a faster reaction relative to cinnamic acid was noted; for compounds with electron-

withdrawing substituents, the opposite was true. Regardless, good yields of the desired β-bromo acids were obtained in all cases. Furthermore, application of the Chapman procedure to these crude acids provided the corresponding diazo ketones, all of which save one were stable compounds. The *p*-methyl substituted diazo ketone **244** proved to be very unstable, decomposing to polymeric material upon standing even in dilute solutions at 0 °C. The ability of the *p*-methyl group to promote ionization of the benzylic bromide is believed to be responsible for this compound's reduced stability. This same effect is more clearly demonstrated in our attempted synthesis of the corresponding *o*-methoxy substituted β-bromo diazo ketone; this derivative could not even be isolated in crude form due to its instability.

Certain β-bromo acid derivatives could not be produced using the hydrobromination reaction. For example, α-methylcinnamic acid was recovered unchanged when treated with the HBr-SiO_2 reagent system. The same result was obtained with other derivatives, such as the 4-nitro and 4-cyanocinnamic acids. In these cases, the alkene appears to be too electron deficient to undergo HBr addition at a reasonable rate.

An alternative route to these b-halo acids with electron-deficient aromatic rings was devoloped based on a benzylic halogenation of the corresponding saturated phenyl-propionic acid derivatives (Table 6). This approach had been successfully employed previously for the bromination of hydrocinnamic acid.[17] As shown in Table 6, sunlamp-irradiation of the hydrocinnamic acids with 1.2 equiv *N*-bromosuccinimide and a catalytic amount of AIBN in refluxing carbon tetrachloride led to the formation of the desired β-bromo acids in good yield; these substrates could be converted to the corresponding diazo ketones as described above by sequential reaction with oxalyl chloride and diazomethane.

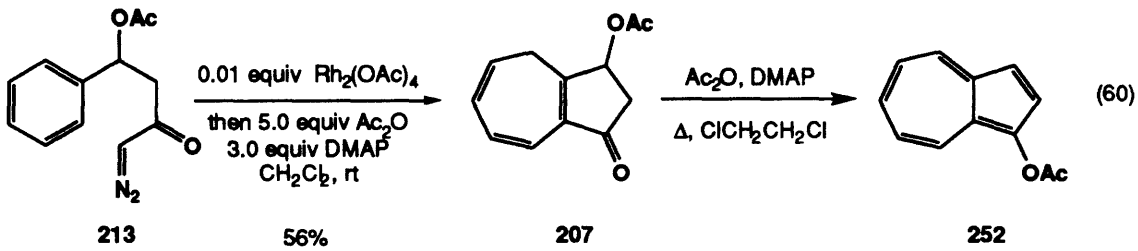
Table 6



entry	hydrocinnamic acid	diazo ketone	% yield
1	**249** (R = H, R' = Me)	**250**	60
2	**251** (R = 4-NO_2, R' = H)	**252**	28
3	**253** (R = 4-CN, R' = H)	**254**	41

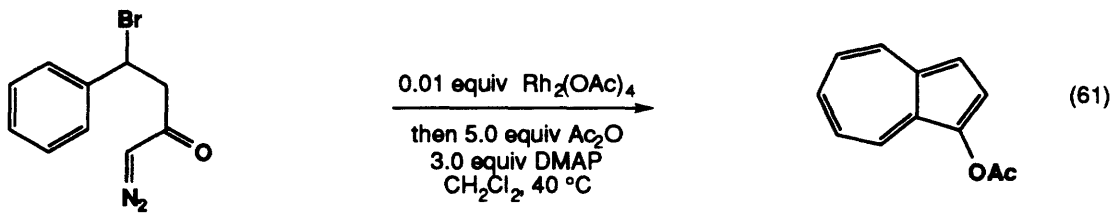
Feasibility of the Ring Expansion-Annulation Reaction

With routes to both the desired β-halo and β-acetoxy diazo ketones in hand, we next turned our attention to testing the validity of our proposed ring expansion-annulation reaction. As detailed in eq 60, treatment of the acetoxy derivative **213** under the standard conditions employed for intramolecular Büchner reactions (slow addition of the substrate to a dilute solution of a catalytic amount of rhodium(II) acetate in refluxing dichloromethane), followed by the addition of acetic anhydride and base did not produce the expected blue color of 1-acetoxyazulene (**252**). Instead, standard workup and purification of the product provided the "alkene isomerization product" hydroazulenone **207**. Although we were able to convertthis material into **252** by extended heating in the presence of excess base and acetic anhydride, this added step was viewed as an unattractive alternative (eq 60).



213 56% 207 252 (60)

In contrast to these results, treatment of the corresponding β-bromo diazo ketone **229** under the standard Büchner reaction conditions followed by the addition of acetic anhydride and base produced a beautiful blue solution (eq 61); after standard workup and purification, a blue solid was isolated. Comparison of the melting point and spectral charateristics of this compound with previously reported data confirmed the identity of this material as 1-acetoxyazulene (**252**).[122]



229 20% 252 (61)

Our initial excitement over the success of this accomplishment was tempered by the low yield obtained for the reaction. We were hopeful, however, that modification of the initial conditions would lead to significant improvements in the efficiency of the reaction.With this reaction as our initial point of reference, we began to explore various options for optimizing the process. We quickly found that the transformation proceeded well at room temperature, although below 0 °C no reaction occurs. Decreasing the temperature from 40 °C to 25 °C led to increases in the yield of approximately 10%. Solvent choice also played an important role in optimizing this reaction. The reaction does occur in Lewis basic solvents (such as diethyl ether) and aromatic solvents (such as

[122]This azulene was previously prepared in 3 steps from azulene by Asao and cowokers; see ref. 62.

benzene); however, TLC analysis of reactions carried out in these solvents indicated the formation of numerous side products. In contrast, reactions performed in dichloromethane were free from most of these contaminants. The addition rate of the diazo ketone substrate and the overall reaction concentration (0.01 M to 0.10 M) appeared to have little significant effect on the outcome of the reaction. Rapid addition (> 3 drops/sec) of the diazo ketone to the catalyst should be avoided, however, as this can lead to decreased yields of azulenes due to carbenoid dimerization. None of these factors appeared to offer much chance to significantly improve the yield of this reaction; the choice of catalyst, however, proved to hold the key to dramatic yield increases.

It has previously been noted that the course of reactions of various rhodium carbenoids derived from α-diazo carbonyl compounds can be altered by varying the ligands attached to the metal center.[123] A number of carbenoid processes which involve rhodium(II) acetate can be dramatically improved by employing more soluble rhodium(II) carboxylates. For instance, rhodium(II) butyrate and rhodium(II) pivalate, which are both much more soluble in organic media than rhodium(II) acetate, have proven to be superior catalysts for a wide variety of cyclopropanation reactions.[124] Varying the metal center's ability to accept electrons can also influence the reactivity and chemoselectivity of the resulting carbenoid. Padwa and Doyle have recently demonstrated that judicious choice of the catalyst can impart chemoselectivity to carbenoid reactions not seen with rhodium(II) acetate.[125] It seemed likely that screening various rhodium(II) catalysts offered a realistic chance to improve the yield of this new azulene forming reaction. As indicated in Table 7, rhodium(II) pivalate provided the dramatic yield increase which we sought. Other catalysts

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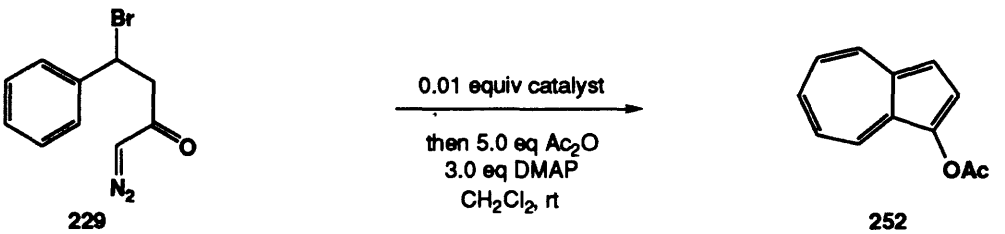
[123]For a recent review see: Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385 and references cited therein.

[124]Doyle, M. P.; Mahapatro, S. N.; Caughey, A. C.; Chinn, M. S.; Colsman, M. R.; Harn, N. K.; Redwine, A. E. Inorg. Chem. 1987, 26, 3070. See also ref 54 a,b.

[125](a)Padwa, A.; Austin, D. J.; Hornbuckle, S. F.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N. *J. Am. Chem. Soc.* **1992**, *114*, 1874. (b) Doyle, M. P.; Pieters, R. J.; Taunton, J.; Pho, H. Q.; Padwa, A.; Hertzog, D. L.; Precedo, L. *J. Org. Chem.* **1991**, *56*, 820. (c) Doyle, M. P.; Westrum, L. J.; Wolthius, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958. (d) Doyle, M. P.; Winchester, W. R.; Hoorn, J. A. A.; Lynch, V.; Simonsen, S. H.; Ghosh, R. *J. Am. Chem. Soc.* **1993**, *115*, 9968.

such as rhodium(II) perfluorobutyrate (entry 1), rhodium(II) triphenylacetate (entry 2), and rhodium(II) octanoate (entry 3) performed no better, and in some cases, worse than rhodium(II) acetate. It was also determined that very little of the metal carboxylate is needed for the ring expansion-annulation reaction. Typically, 1 mole percent of the catalyst was employed for reactions of this type, but as little as 0.1 mole % rhodium(II) pivalate accomplished the task with no detrimental effect on the yield. We were indeed delighted to find that rhodium(II) pivalate provided such excellent results, as we expected an added benefit from this catalyst. Previous work in our group by Koyama had demonstrated that this catalyst was capable of promoting regioselective intramolecular Büchner reactions in the saturated series, presumably due to the bulky pivalate ligands of the carbenoid (eq 62). For example, the reaction of diazo ketone **265** with rhodium(II) trifluoroacetate provided a 3:1 mixture of the two regioisomers **266** and **267**. The use of rhodium(II) pivalate, however, provided **266** as the sole product from this reaction.[126] We believed that similar selectivities would be possible for our system.

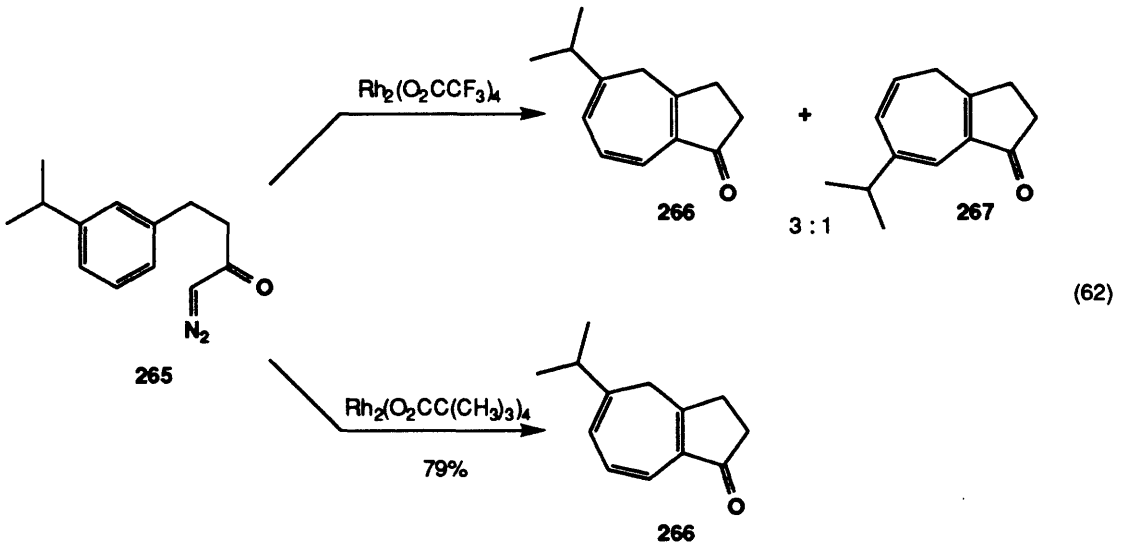
Table 7



229 **252**

CATALYST	% YIELD
$Rh_2(O_2CC_3F_7)_4$	19
$Rh_2(O_2CCPh_3)_4$	30
$Rh_2(O_2CC_7H_{15})_4$	38
$Rh_2(OAc)_4$	20-46
$Rh_2(OCO\text{-}t\text{-}Bu)_4$	72

[126]Koyama, H.; Danheiser, R. L., unpublished results.



(62)

Scope of the Ring Expansion-Annulation Reaction

Having determined the optimal conditions for the key ring expansion-annulation reaction, we turned our attention toward defining the scope and limitations of this new process; Table 8 summarizes our results. All of these reactions save one (entry 5, *vide infra*) were carried out under the optimal conditions: slow addition over 15-45 min of the substrate (1 drop/4 sec) to a dilute solution of a 0.01 equiv of rhodium(II) acetate in dichloromethane at room temperature, followed by the addition of 5.0 equiv of acetic anhydride and 3.0 equiv of 4-dimethylaminopyridine. We have demonstrated that this ring expansion-annulation process is fairly general in nature and tolerates the incorporation of both electron-donating substituents (such as alkyl groups, entries 2,5,8) and various electron withdrawing groups (such as nitro and cyano functions, entries 10,11) on the aromatic ring. The ability of this method to produce various halogenated azulenes (entries 3,4,6,9,12) stands in direct contrast to earlier reports on the feasibility of intramolecular Büchner reactions on haloarenes.

Table 8

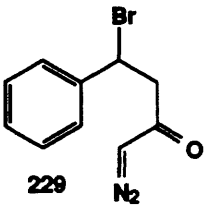
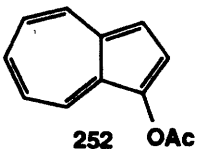
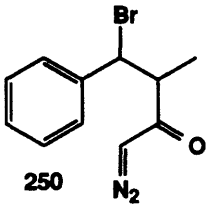
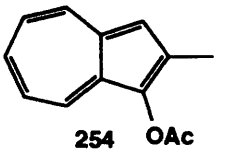
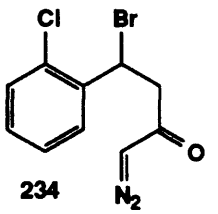
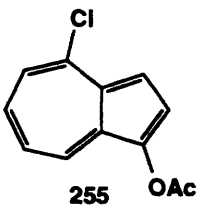
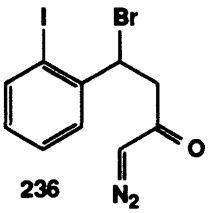
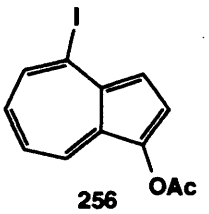
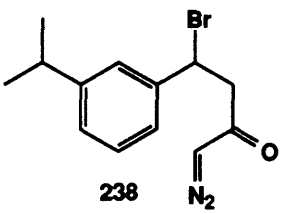
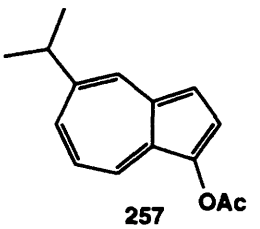
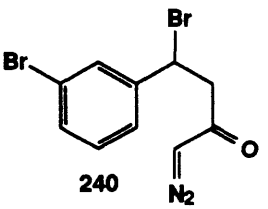
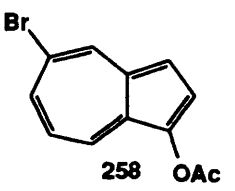
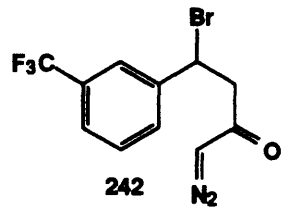
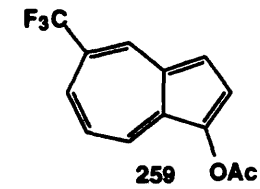
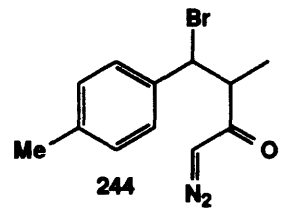
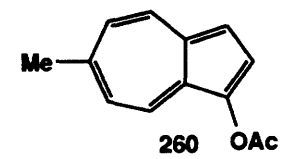
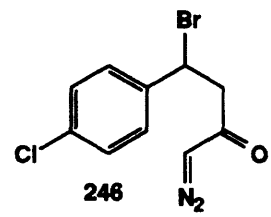
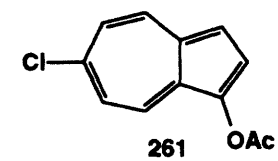
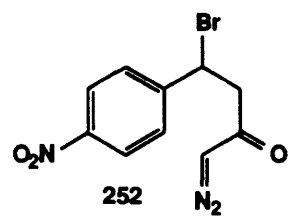
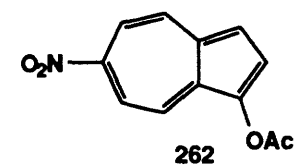
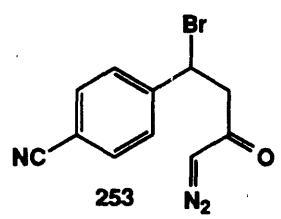
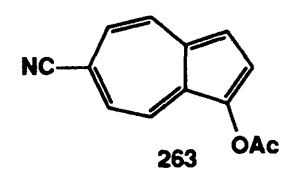
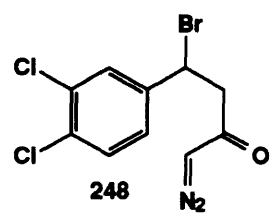
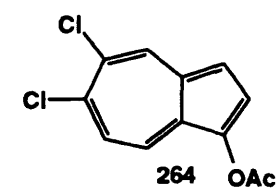
Entry	Starting Material	Azulene	Yield (%)
1	 229	 252	65-72
2	 250	 254	58
3	 234	 255	61
4	 236	 256	68
5	 238	 257	53
6	 240	 258	39

Table 8 (cont)

Entry	Starting Material	Azulene	Yield (%)
7	 242	 259	40
8	 244	 260	47
9	 246	 261	61
10	 252	 262	21
11	 253	 263	39
12	 248	 264	19

In his *Organic Syntheses* preparation, Scott reported that the Büchner reaction failed for substrates which were halogenated on the aryl ring.[59,127] We have also found that our reaction allows for the synthesis of polysubstituted azulenes, as exemplified by entry 12, although this aspect of the process had not been fully explored. However, as shown in Scheme 34, certain β-bromo diazo ketones do not undergo the ring expansion-annulation reaction to provide azulenes. Treatment of the α-naphthyl[128] or *m*-silyloxy[129] substituted cases with rhodium(II) pivalate leads to complex mixtures of products, none of which are azulenes. The 3,5-difluoro[130] case does furnish azulenic material in low yields when treated under the standard reaction conditions, however, the identity of these azulenes has not been determined. Subtle changes in the electronic nature of the aromatic ring caused by these substituents may be responsible for their failure to undergo the expected reaction.

Curiously, the *m*-isopropyl derivative **238** also does not provide azulenes when treated under the standard reaction conditions for this ring expansion-annulation. Exposure of **238** to rhodium(II) pivalate in dichloromethane results in the formation of β-naphthol **271** (eq 63). We originally thought that this product was formed due to a trace amount of acid in the reaction mixture (possibly from premature elimination of HBr from one of the reaction intermediates). The inclusion of acid scavengers such as calcium carbonate, methyltrimethoxysilane, and poly(4-vinylpyridine), however, did not change the outcome of the reaction. Although we are unable to explain why the reaction does not furnish azulenes when performed in dichloromethane, we were able to ultimately effect the desired transformation by simply conducting this reaction in diethyl ether.

---

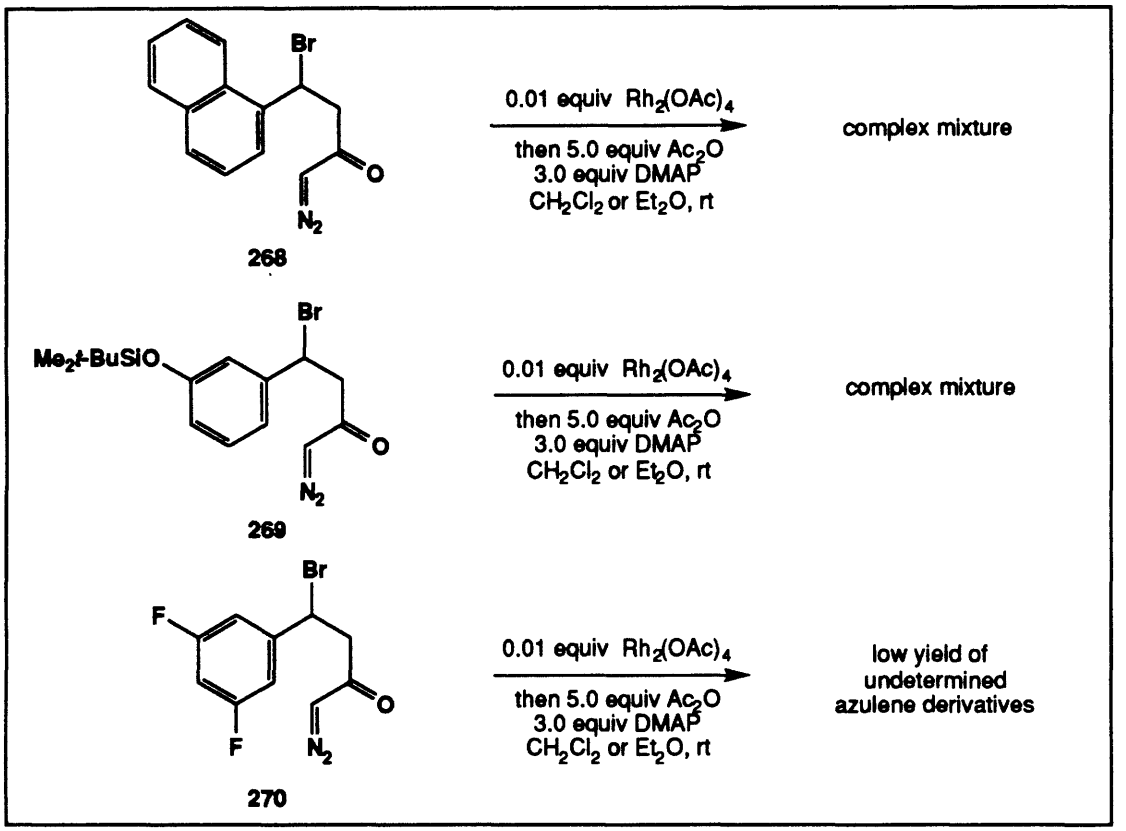
[127]Scott's report seems rather peculiar, however, considering other groups have reported Büchner-type reactions of haloarenes. For examples, see: (a) Hrytsak, M. Durst, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1150. (b) Doyle, M. P.; Shanklin, M. S.; Oon, S. -M.; Pho, H. Q.; van der Heide, F. R.; Veal, W. R. *J. Org. Chem.* **1988**, *53*, 3386. (c) Doyle, M. P.; Shanklin, M. S.; Pho, H. Q. *Tetrahedron Lett.* **1988**, *29*, 2639.

[128]This derivative was synthesized from 3-(1-naphthyl)acrylic acid in 3 steps (HBr addition, followed by treatment with oxalyl chloride and diazomethane) in 50% yield.

[129]This derivative was synthesized from 3-(3-hydroxyphenyl)propionic acid in 4 steps (silylation with TBDMSCl, NBS bromination, followed by treatment with oxalyl chloride and diazomethane) in 54% yield.

[130]This derivative was synthesized from 3-(3,5-difluorophenyl)propionic acid in 3 steps (NBS bromination, followed by treatment with oxalyl chloride and diazomethane) in 64% yield.

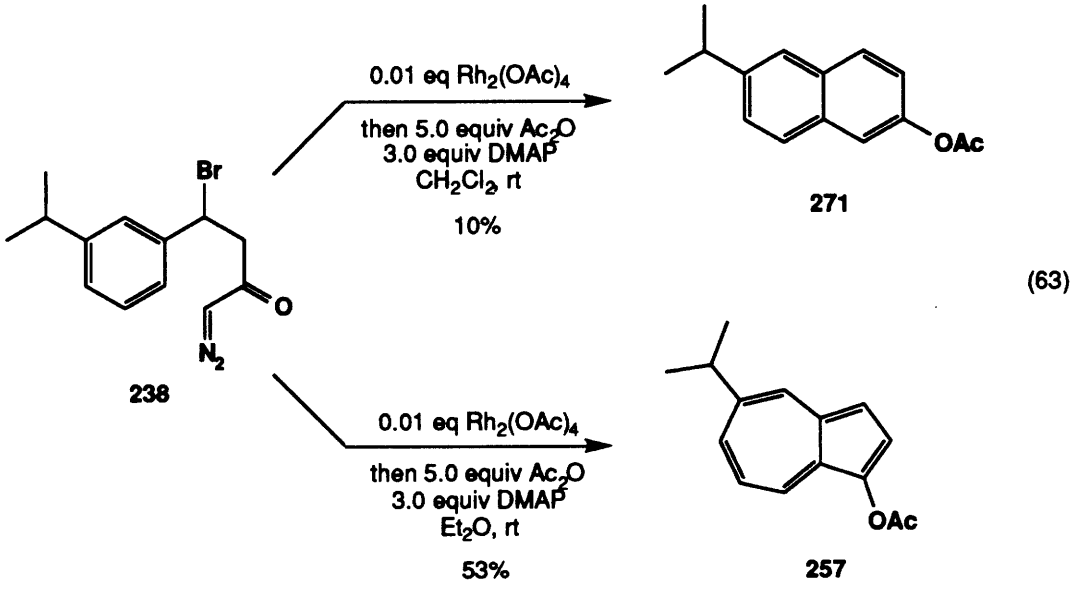
Scheme 34



When run in this solvent, however, at least 1 mole percent of the catalyst is required, and the reaction requires significantly more time for complete consumption of starting material (30-45 min versus 10-15 min for reactions performed in dichloromethane). These observations indicate that the diethyl ether is playing an important part in determining the path of the reaction, although at this time its role is unknown.

For the most part, yields for these reactions are fairly good (Table 8), with some notable exceptions. Deactivating the aryl ring by incorporating electron withdrawing substituents (e.g. 4-nitro, 3,4-dichloro) significantly reduces the amount of azulene that is formed. These cases tend to provide large amounts of byproducts (presumably through carbenoid dimerization). It is possible that a more reactive carbenoid, such as one generated with rhodium(II) perfluorobutyrate, would increase yields for these cases;

however, given its poor performance for the unsubstituted case, no guarantee exists that this catalyst can overcome the problem.



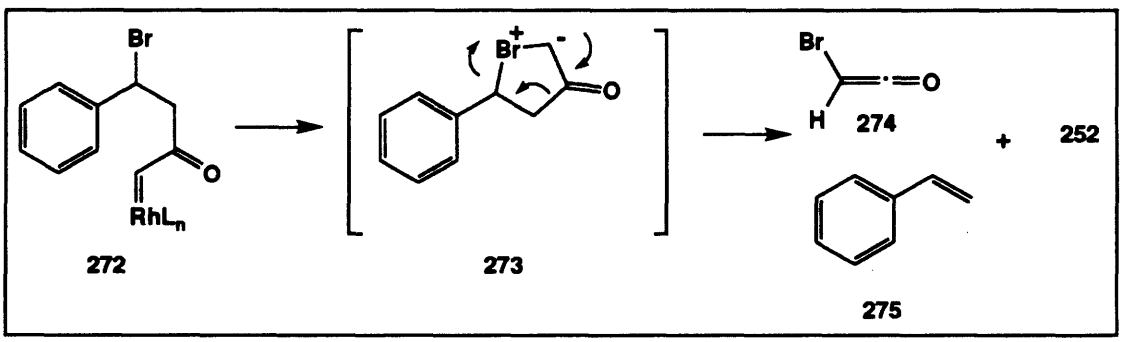
(63)

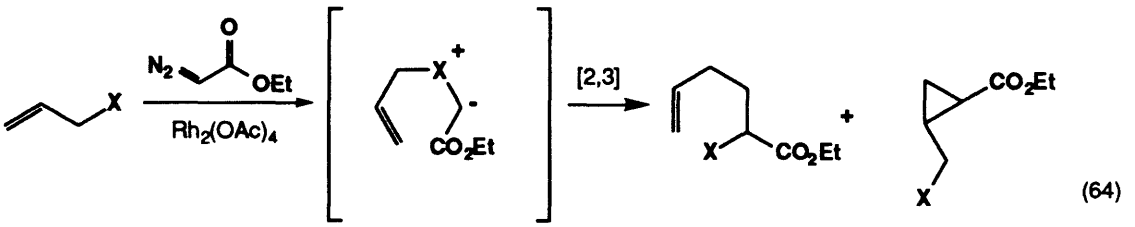
As previously mentioned, the ring expansion-annulation process tends to be a very clean reaction. In all cases, however, one major contaminant, proven to be a styrene derivative by spectroscopic analysis, can be isolated from the reaction mixture in 10-15% yield. We believe this material arises as shown in Scheme 35. Interception of the rhodium carbenoid species **272** by the β-bromine atom can lead to an ylide intermediate **273**. We suggest that this intermediate is responsible for the formation of the styrene byproduct via fragmentation to give **275** and bromoketene (**274**). Although no trace of **274** or any of its reaction products has been observed in the crude reaction mixture, ample precedent for the formation of ylides from rhodium carbenoids and heteroatoms exists. For instance, Doyle and coworkers proposed that a related ylide was formed when various allylic halides were exposed to the rhodium carbenoid of ethyl diazoacetate (eq 64).[131] In fact, this group found that the amount of the ylide formed varied with the identity of the allylic halide. For

[131]Doyle, M. P.; Tamblyn, W. H.; Bagheri, V. *J. Org. Chem.* **1981**, *46*, 5094. See also Bailey, R. J.; Shechter, H. *J. Am. Chem. Soc.* **1974**, *96*, 8116.

allyl iodide, the sole product isolated from the reaction mixture was **278**, a product of ylide formation and subsequent [2,3] sigmatropic rearrangement. Allyl bromide behaved rather differently. In this case, cyclopropanation is the dominant reaction pathway, and only small amounts of **278** were isolated. Interestingly, a significant drop in ylide formation is observed when allyl chloride is the substrate; this reaction gave less than 5% of **278**. While providing us with the precedent we were searching for, this paper also suggested to us that we could limit or eliminate styrene formation in our reaction by employing a β-chloro diazo ketone. In fact, however, treatment of **280** under our Büchner reaction conditions not only did not suppress styrene formation, but the yield of the azulene derivative was also lower.

Scheme 35

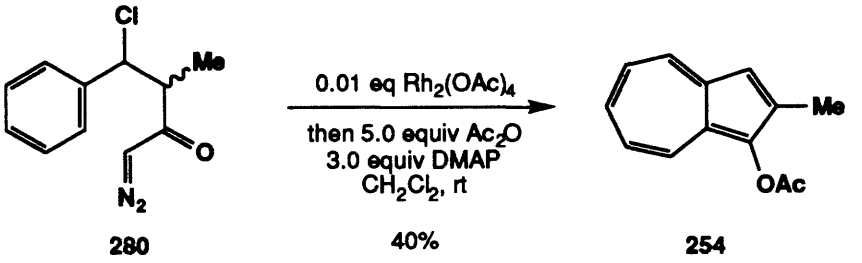




276a, X = I
276b, X = Br
276c, X = Cl

277a-c **278a-c** **279a-c**

X	ratio 278:279
I	100:0
Br	27:73
Cl	5:95

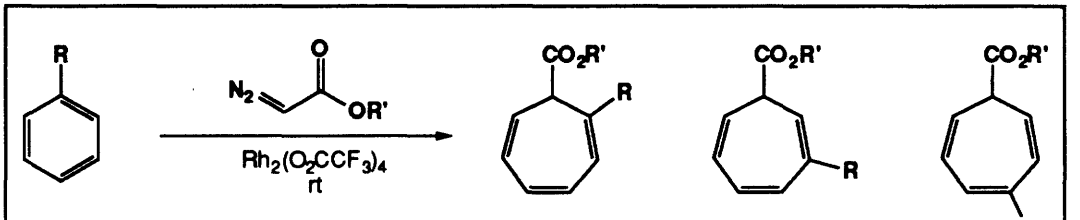


280 40% 254 (65)

Regiochemistry of the Ring Expansion-Annulation Reaction

Previous literature examples of both the intermolecular and intramolecular Büchner reactions have demonstrated that these processes are regioselective. As shown in Scheme 36, Noels and Hubert have found that in the intermolecular Büchner reaction of various Rh(II) carbenoids of α-diazo esters with substituted aromatics, little or no cycloaddition occurs at the site of greatest steric congestion.[55b] Thus, cycloheptatrienes **61f** and **61g** are formed preferentially to **61e**. The regioselectivity appears to be due to a steric effect, as demonstrated by the results of the reaction of toluene with both methyl and *t*-butyl diazoacetate. The electronic nature of the substituent does not seem to play a major role in determining the regiochemical outcome of the reaction.

Scheme 36



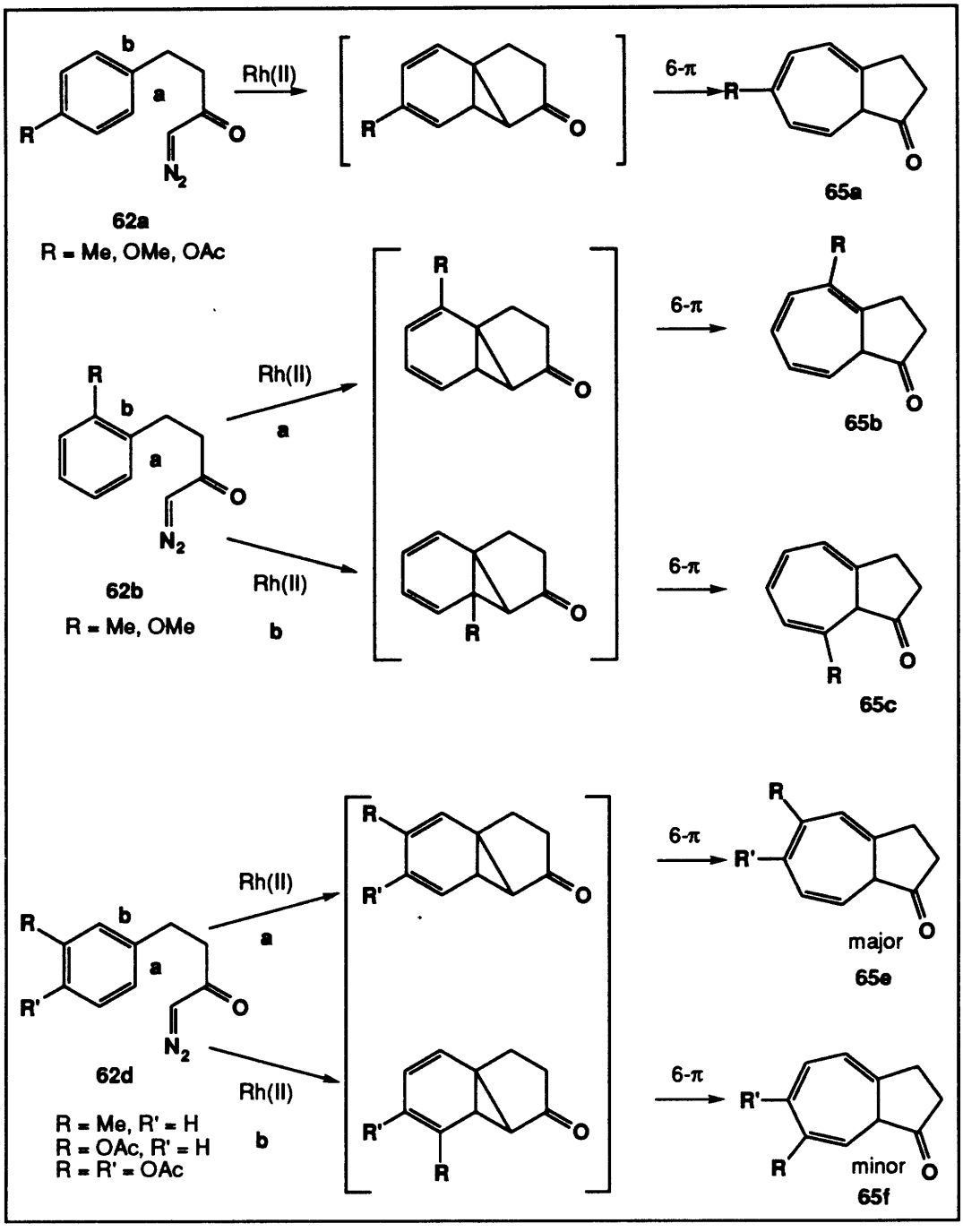
	61 e	61f	61g
R = Me, R' = Me	17	23	56
R = Me, R'= *t*-Bu	0	13	32
R = OMe, R' = Me	0	8	56
R = Cl, R' = Me	5	15	80

McKervey and Scott have shown that the regiochemical course of the intramolecular Büchner reaction is also well defined.[54,56,57a] Scheme 37 shows that the reaction of diazo

ketones which bear a *para* substituent on the aromatic ring provides only one product, since cycloaddition at either site **a** or site **b** gives the same norcaradiene intermediate. However, the reactions of diazo ketones which bear substituents at either the *ortho* or *meta* position on the aromatic ring can, in theory, lead to the formation of regioisomers.

McKervey found that for *o*-substituted cases, only one product is obtained from the Büchner reaction, but the isomer that is formed depends upon the nature of the substituent. As expected, the *o*-methyl substituted case furnishes **65b**, indicating that the cycloaddition occurs away from the site of substitution. However, for the *o*-methoxy derivative, McKervey originally reported that the cycloaddition occurs at the *more hindered* site to give **65c**. McKervey suggested that this product was formed due to chelation of the Rh(II) carbenoid by the OMe group. This results seems rather odd considering that this effect was not seen in the intermolecular Büchner reaction of Rh(II) carbenoids with anisole. In fact, Cordi and coworkers were able to prove through the use of high field ^{1}H NMR that the product from McKervey's reaction is not **65b** but rather **65c**, thus further validating the original steric argument of Noels and Hubert.[57b] The results of the intramolecular Büchner reaction of various *m*-substituted diazo ketones follow the general trends seen in other cases. McKervey has found that the reaction of these substrates provides **65e** as the major product, indicating that the cycloaddition occurs away from the site of higher steric congestion.

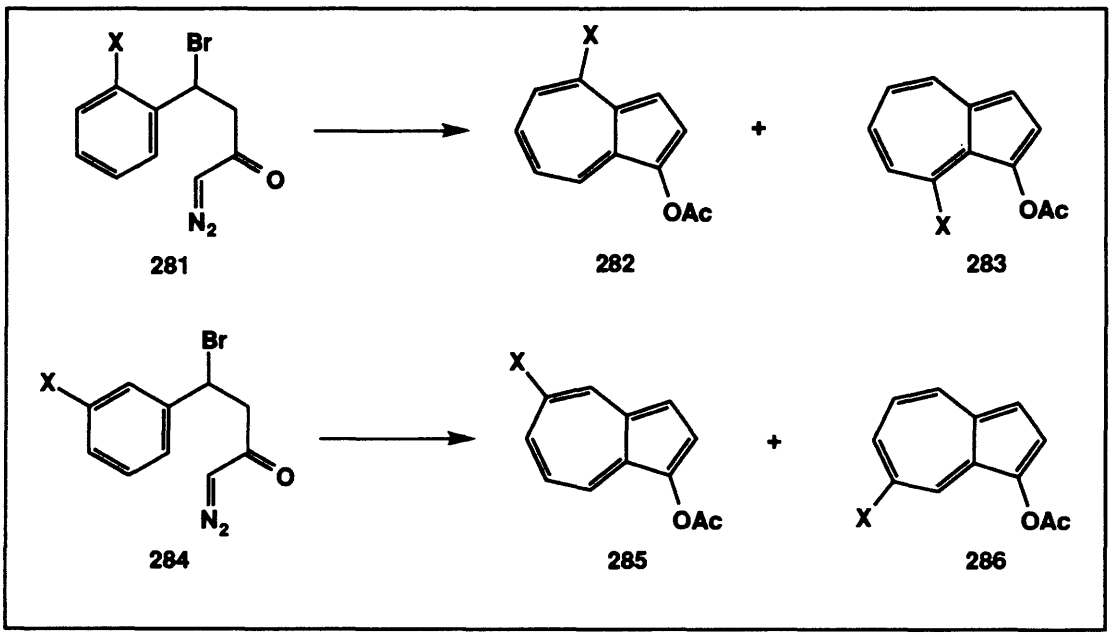
Scheme 37



Based on the previous literature examples, we expected that our new ring expansion-annulation approach to substituted azulenes would be highly regioselective. For β-bromo diazo ketones which incorporate substituents *alpha* to the carbonyl group (e.g., **250**) or *para* on the aromatic ring (e.g., **244**), only one regioisomer can be formed (*vide*

supra). This was confirmed by comparison of the ^1H NMR data of the products obtained from these reactions with the ^1H NMR data of the known 1-acetoxyazulene.[62] On the ohter hand, substrates which are substituted in either the *ortho* or *meta* positions on the aromatic system can result in formation of regioisomeric azulenes (Scheme 38).

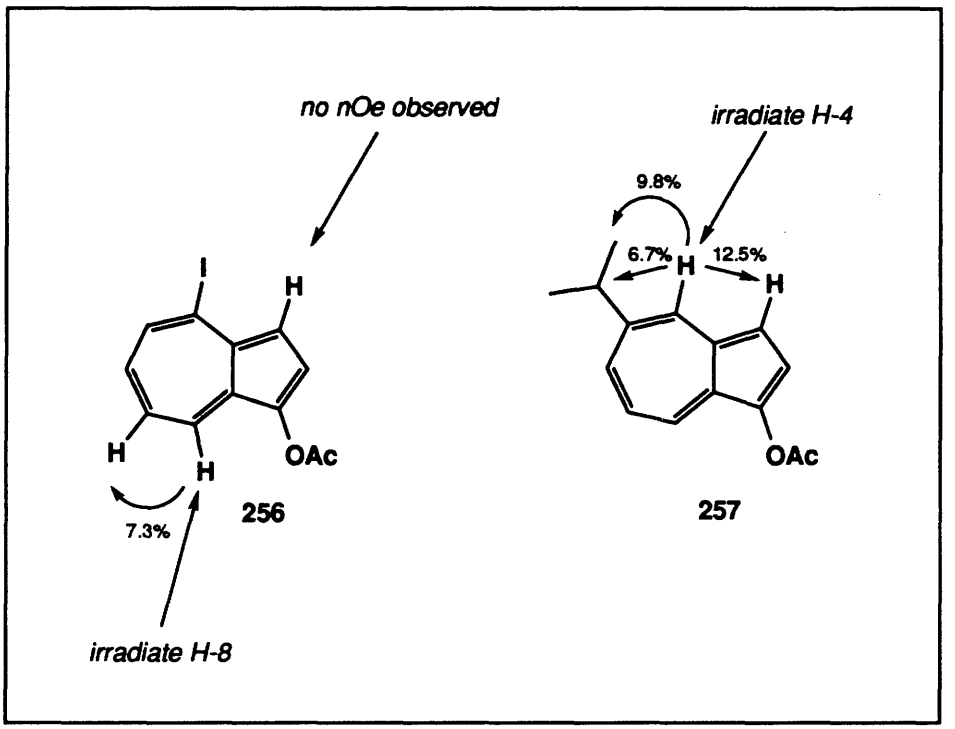
Scheme 38



As demonstrated in entries 3 and 4 of Table 8, we observed that the *o*-substituted diazo ketones provide a single isomer when exposed to rhodium(II) pivalate; nOe experiments on **256** proved that the 1,4-disubstituted derivative is formed under these conditions (Figure 2). This regioselectivity can be explained by invoking the same steric argument reported above. The initial cycloaddition of the rhodium carbenoid, with its bulky pivalate ligands, to the aryl system prefers to occur away from the *ortho* group, independent of the size of the substituent. Thus, the 1,4-isomer is formed. More evidence for this steric argument is provided by the *m*-substituted cases. Here, the bulk of the *meta* substituent appears to play a crucial role in determining the site of the carbenoid cycloaddition. For example, the *m*-isopropyl substituted diazo ketone **238** furnishes only one isomer upon reaction with

rhodium(II) pivalate, and nOe studies of the product of this reaction confirm it to be the 1,5-regioisomer **257** (Figure 2). Diazo ketone **248**, with a relatively small *m*-chlorine atom, provides a 19:1 ratio (as judged by ^{1}H NMR) of two regioisomers. Using the *m*-isopropyl case as a model, the major product was assigned as the 1,5,6-isomer (entry 12, Table 8) while the minor product is the corresponding 1,6,7-isomer. Other diazo ketones, such as the *m*-bromo derivative **240** and the *m*-trifluoromethyl derivative **242**, give almost exclusively the 1,5-regioisomer, as confirmed by comparison of the ^{1}H spectra for the corresponding azulenes **258** and **259** with the ^{1}H NMR data for **252** and **257**. For these cases, a trace (<1%) of another azulene (assumed to be the 1,7-isomer) can be observed by TLC of the crude reaction mixture.

Figure 2



Summary

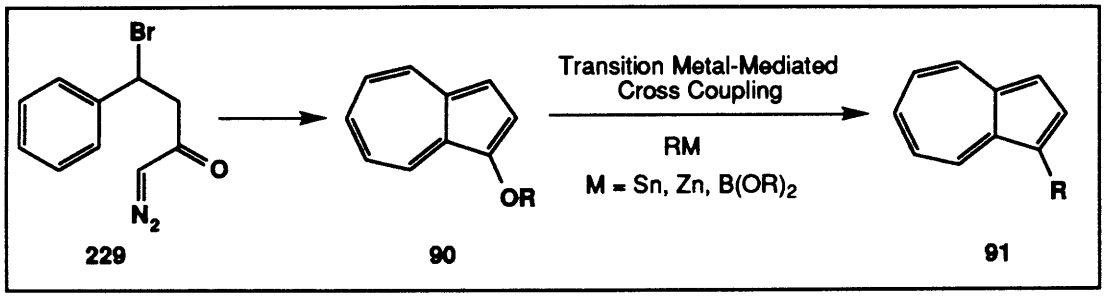
This chapter has detailed the conception, realization, and development of a new ring expansion-annulation approach to substituted azulenes. This process has the ability to efficiently create substituted 1-hydroxyazulene derivatives, with good to excellent regiochemical control over substituents on both the five- and seven-membered rings. In fact, this method represents the only general strategy available to synthesize this interesting but relatively unknown class of azulenes. The problems that limit most of the classical approaches to substituted azulenes (e.g. exotic starting materials, harsh reaction conditions, lack of regiochemical control) are largely overcome by this method. The presence of the 1-hydroxy functionality in the products of our annulation would appear to make this method ideally suited for the synthesis of various azulenoquinone derivatives. Furthermore, modification of this new process may allow for its use in the construction of various polysubstituted azulenes, including polycyclic and heterocyclic derivatives. Studies investigating the synthetic utility of these 1-hydroxyazulene derivatives have begun in our laboratories; the preliminary results are presented in the following chapter.

CHAPTER 4

Synthetic Utility of 1-Hydroxyazulenes Derivatives

As detailed in Chapter 3, our new ring expansion-annulation approach to substituted azulenes via β-bromo diazo ketones allows for the construction of various functionalized 1-hydroxyazulene derivatives, most of which cannot be made utilizing classical methods. For this reason alone, our strategy should be recognized as a significant contribution to the science of azulene synthesis. The preparation of hydroxyazulenes, however, was only one of our original goals in this project (Scheme 39). As discussed earlier, we hoped that these interesting azulene derivatives would serve as versatile intermediates providing access to a wide array of functionalized azulenes via transition metal-mediated cross coupling reactions. In this chapter, the synthesis of azulene triflates will be discussed, along with the results of various cross coupling reactions on these substrates. In addition, the synthesis of the anti-ulcerative *Azuletil sodium*, showcasing both the ring-expansion-annulation strategy and cross coupling techniques, will be presented.

Scheme 39

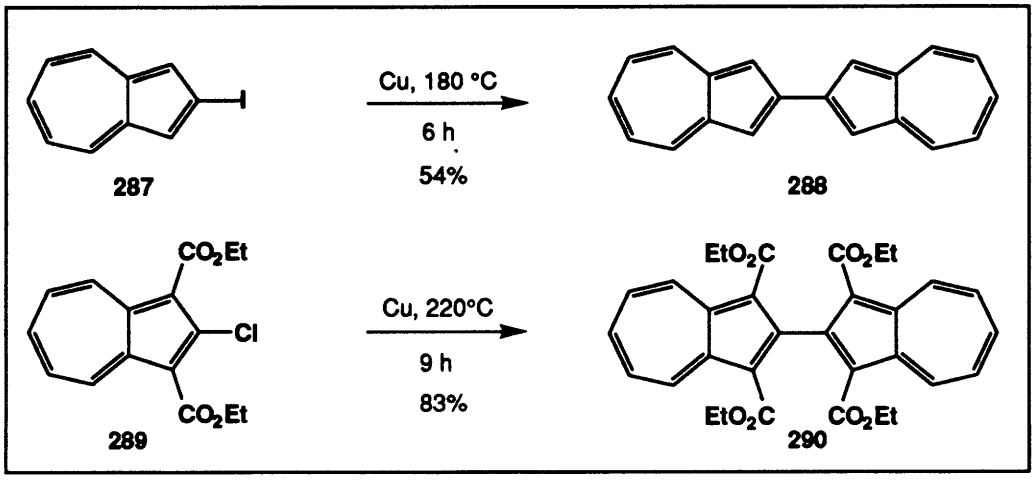


Azulene Cross Coupling Reactions

Transition metal-mediated cross coupling reactions of organic electrophiles (such as aryl halides and sulfonates) with various organometallic partners have been used extensively in synthesis.[132] Many researchers view these methods as among the most powerful tools available to the organic chemist for the formation of C-C bonds. In most cases, reactions of this type proceed under mild conditions, with high tolerance of sensitive functionality and with little regard for steric hindrance; yields are also generally quite high. Given that cross coupling protocols are applicable to a wide variety of aromatic and heteroaromatic systems, we were surprised to find that only a few reports of cross coupling reactions involving the azulene ring system have appeared in the literature.

In 1982, Morita and Takase demonstrated that various haloazulenes would undergo Ullman-type reactions to give coupled products (Scheme 40).[133]

Scheme 40



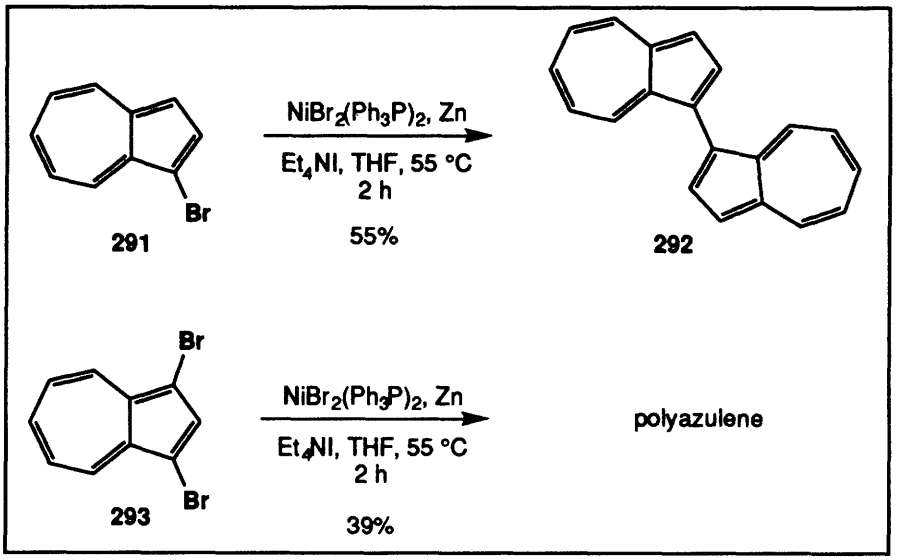
[132]For excellent general reviews of cross coupling reactions involving aryl halides and sulfonates, see: (a) Tamao, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 3, p 435. (b) Knight, D. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 3, p 481. (c) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 3, p 521. (d) Ritter, K. *Synthesis* **1993**, 735. (e) Sainsbury, R. *Tetrahedron* **1980**, *36*, 3327.

[133]Morita, T.; Takase, K. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1144.

For example, heating 2-iodoazulene (**287**) with activated copper leads to the formation of 2,2'-biazulene (**288**). This method can be employed for the synthesis of various other biazulenes in good to excellent yield, but in all cases the reaction conditions are rather harsh. Furthermore, this procedure is generally limited to iodoazulene derivatives, although the incorporation of multiple electron withdrawing substituents allows the chloroazulene derivative **289** to undergo this reaction.

Several years later, Iyoda and coworkers demonstrated that a facile homocoupling of haloazulenes takes place in the presence of a catalytic amount of a zerovalent nickel complex.[134] As shown below in Scheme 41, 1-bromoazulene (**291**) participates in a homocoupling reaction under these conditions to furnish 1,1'-biazulene (**292**). This method is an excellent choice for the synthesis of various bi-, ter-, and polyazulenes, as the yields are generally good and the reaction conditions are quite mild.

Scheme 41

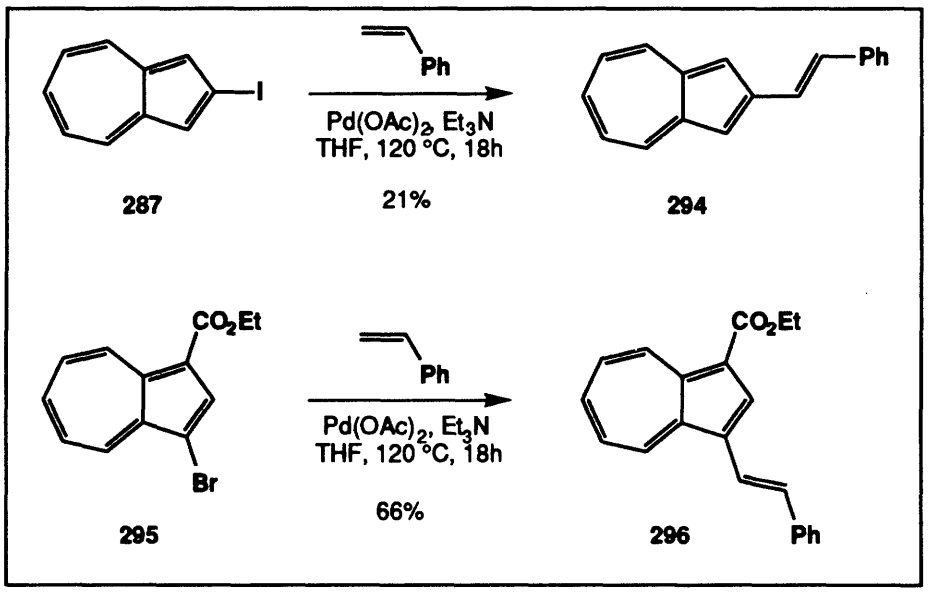


Recently, Horino and coworkers have reported the use of haloazulenes in Heck reactions (Scheme 42).[135] For instance, 2-iodoazulene (**287**) will couple to styrene in the presence of palladium acetate, albeit in low yield. This example is indicative of one of

[134]Iyoda, M.; Sato, K.; Oda, M. *Tetrahedron Lett.* **1985**, *26*, 3829.
[135]Horino, H.; Asao, T.; Inoue, N. *Bull. Chem. Soc. Jpn.* **1988**, *64*, 183.

the major difficulties encountered in the cross coupling reactions of haloazulenes. It has been well established that transition metal-mediated cross couplings of electron rich aryl halides are more difficult than the corresponding reactions on electron poor substrates.[135] Since the five-membered ring of an azulene is electron rich, it is reasonable to expect that reactions of this type with 1-, 2-, or 3-haloazulenes should be difficult. Incorporating substituents that are capable of withdrawing some of this electron density, however, should be beneficial to the cross coupling reaction. Indeed, 1-bromo-3-carboethoxyazulene (**295**) undergoes a Heck reaction to give the styrene derivative **296** in good yield.

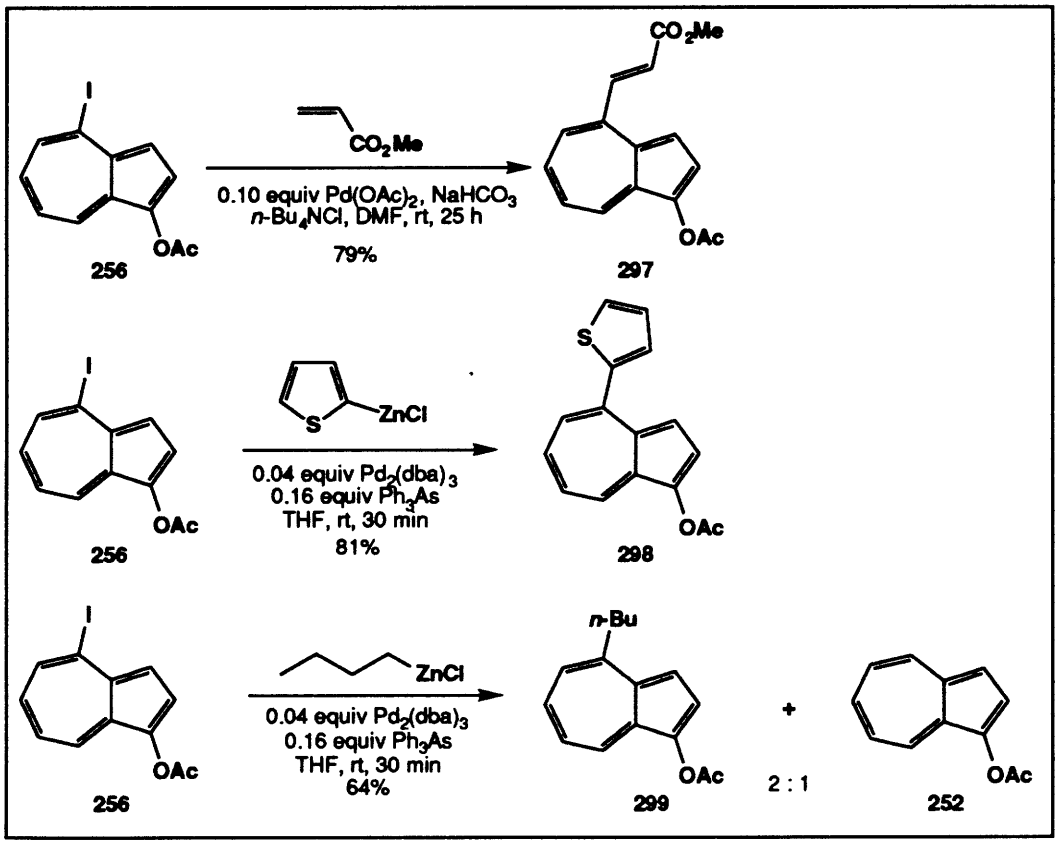
Scheme 42



Since the seven-membered ring of an azulene is electron deficient compared to the five-membered ring, cross coupling reactions of azulenes halogenated in positions 4 through 8 should occur more readily than ones halogenated in positions 1 through 3. To test this hypothesis, we examined various palladium catalyzed reactions of the iodoazulene derivative **256** which we synthesized using our ring expansion-annulation strategy. As outlined in Scheme 43, treatment of this compound under Jeffrey's modified Heck reaction conditions[64] led to the formation of the acrylate derivative **297** in high

'ield. Note that no additional electron-withdrawing functionality is required for :xcellent results. Furtheremore, this process is much milder than the one previously :mployed by Horino. The iodoazulene **256** also couples with aryl and alkylzinc eagents[136] to give high yields of coupled products; treatment of 256 with either zinc eagent in the presence of a catalytic amount of tris(dibenzylideneacetone)dipalladium nd triphenylarsine at room temperature in tetrahydrofuran provides the desired products n good yields. However, the latter process is accompanied by the concomitant formation)f 1-acetoxyazulene (**252**) via a β-hydride elimination process that competes with the desired reaction. The catalyst system employed in these two zinc-based cross couplings will be discussed in a later section of this chapter.

Scheme 43

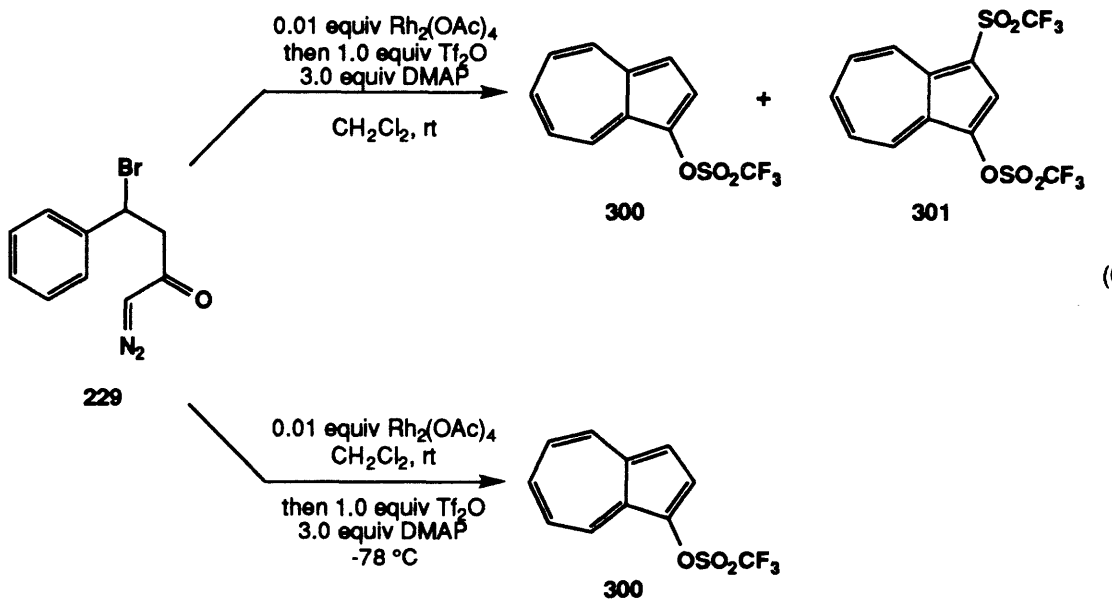


[136]For a recent review of cross coupling reactions with organozinc reagents, see: Erdik, E. *Tetrahedron* 992, *48*, 9577.

These examples demonstrate that cross coupling reactions of azulenes halogenated on the seven-membered ring are indeed facile. Furthermore, since our azulene forming reaction has the ability to produce derivatives with halogens at specific positions on the seven-membered ring, by combining this method with various transition metal-mediated cross coupling reactions it is possible to produce substituted a wide variety of azulenes.

Synthesis of Azulene Triflates

The initial attempts to form the azulene triflate derivative **300** using our new method simply involved changing the trapping reagent from acetic anhydride to trifluoromethanesulfonic anhydride (eq 65).[137] However, under the standard ring expansion-annulation reaction conditions, the addition of triflic anhydride at 25 °C led to the formation of the desired triflate derivative **300**, contaminated with several other more polar azulene byproducts. It is reasonable to assume that at this temperature electrophilic substitution of the C-3 position occurs, giving rise to **301**.



(65)

[137]For reviews on the synthesis of aryl triflates, see: Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85 and ref. 129d.

Fortunately, by reducing the temperature of the trapping step a much cleaner reaction is observed. Thus, by cooling the reaction mixture to -78 °C prior to the addition of triflic anhydride and 4-dimethylaminopyridine, the sole azulene product obtained is **300**. Standard workup and purification by flash chromatography provides **300** as a purple-blue oil. The ^{1}H NMR spectra of the azulene triflate **300** and 1-acetoxyazulene (**252**) are dramatically different. Only H-4 and H-8 are well defined in the 300 MHz spectrum of **300**; the remaining five protons are grouped into two multiplets, with H-5, H-6, and H-7 showing downfield shifts relative to **252**. In contrast, all seven aromatic protons of **252** are well resolved at 300 MHz. It seems reasonable to expect that the properties of **300** and **252** would be radically different based on the information provided above.

In neat form, **300** exhibits a remarkable propensity to undergo a rapid polymerization to provide a black intractable solid. Initially, we believed that traces of triflic acid were surviving the purification steps and promoting polymerization of the triflate. Taking steps to rigorously exclude all traces of acid, such as including 1% triethylamine in the chromatography eluant, did not seem to affect the stability of **300**, thereby indicating that **300** may be inherently unstable. We currently believe that **300**, like 1-hydroxyazulene (*vide supra*), is extremely susceptible to phenolic-type oxidation, as shown below in Scheme 44. An electron transfer reaction between **300** and O_2 should be a facile process, since the radical cation intermediate **300a** has tropylium-like character. We believe that this species may be susceptible to S-O bond cleavage by nucleophilic attack on the triflate group, leading to polymerization of **300b** by phenolic coupling reactions. Similar mechanisms have been suggested for the autoxidation of various alkyl azulene derivatives.[138] The triflate derivative **300** is stable in inert solvents

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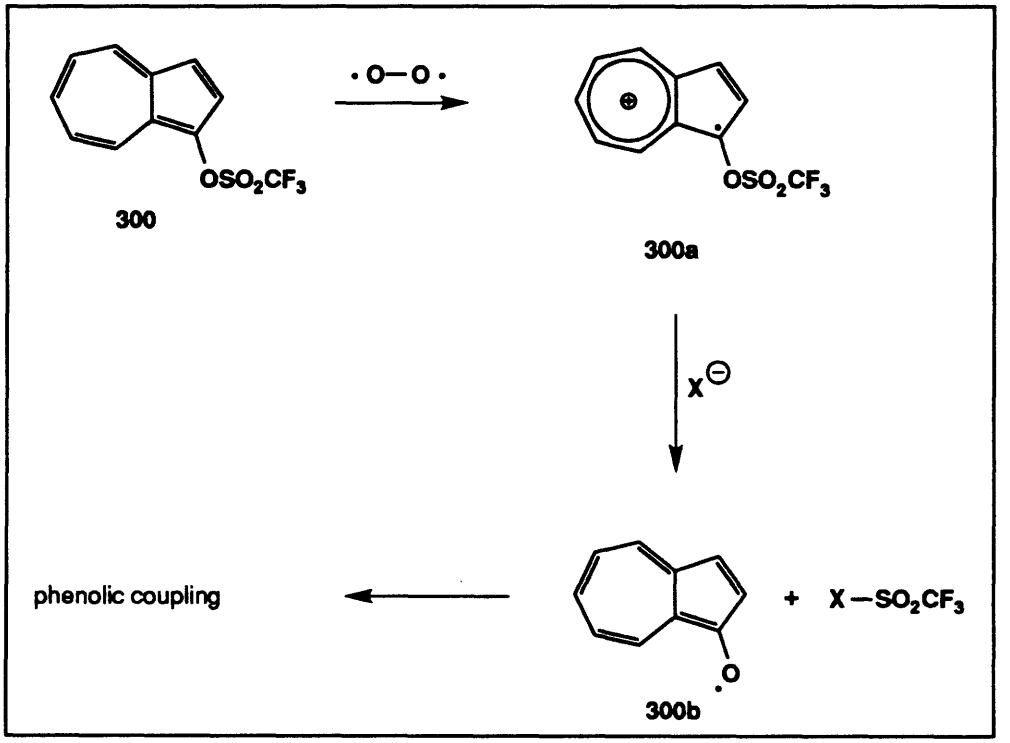
[138](a) Nozoe, T.; Takekuma, S.; Doi, M.; Matsubara, Y.; Yamamoto, H. *Chem. Lett.* **1984**, 627. (b) Matsubara, Y.; Takekuma, S.; Yokoi, K.; Yamamoto, H.; Nozoe, T. *Chem. Lett.* **1984**, 631. (c) Matsubara, Y.; Takekuma, S.; Yamamoto, H.; Nozoe, T. *Chem. Lett.* **1987**, 455. (d) Matsubara, Y.; Takekuma, S.; Yokoi, K.; Yamamoto, H.; Nozoe, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1415. (e) Takekuma, S.; Matsubara, Y.; Yamamoto, H.; Nozoe, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3721. (f) Takekuma, S.; Matsubara, Y.; Yamamoto, H.; Nozoe, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 475. (g) Matsubara, Y.; Morita, M.; Matsui, S.; Takekuma, S.; Yamamoto, H.; Ito, S.; Morita, N.; Asao, T.; Nozoe, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1841.

(such as dichloromethane and carbon tetrachloride) and can be stored at -78 °C for several weeks without significant decomposition.

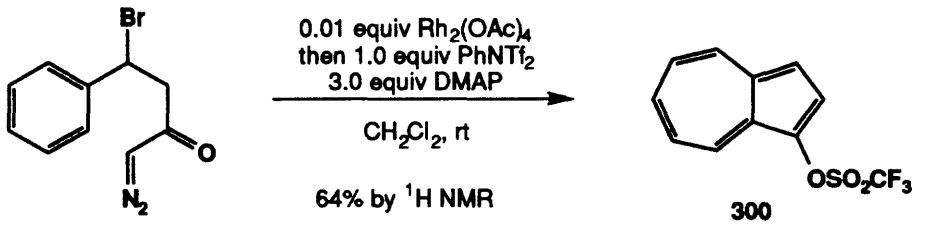
Scheme 44



In addition to triflic anhydride, we have examined the ability of other triflating reagents to trap 1-hydroxyazulenes. *N*-Phenyltriflimide,[139] a stable, non-hygroscopic solid triflating reagent, consistently provides **300** in good yield at room temperature (eq 66).[140] However, the purification of the resulting triflate is more difficult when *N*-phenyltriflimide is employed, as it co-elutes with the desired product.

[139]Hendrickson, J. B.; Bergeron, R. *Tetrahedron Lett.* **1973**, 4607.

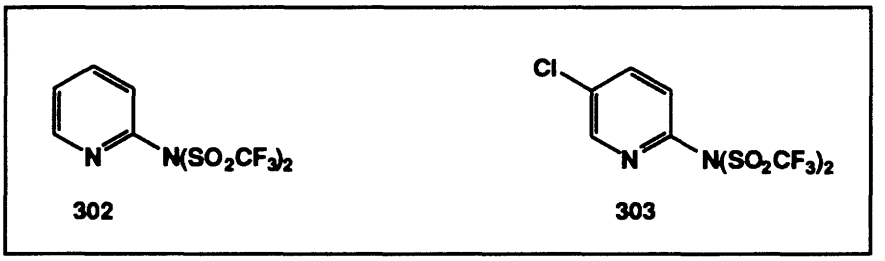
[140]Since azulene triflate **300** is unstable in concentrated form, this yield was determined by ^{1}H NMR.



229 300 (66)

We have found that most of the excess *N*-phenyltriflimide can be removed by simply treating the crude reaction mixture with piperidine, followed by standard aqueous workup. Recently, Comins has reported that similar pyridine-based triflimides **302** and **303** (Scheme 45) are more reactive triflating reagents and easier to separate from the reaction mixture by an acidic workup.[141] Unfortunately, when **303** is employed in our reaction, TLC indicates that a significant amount of electrophilic substitution at the C-3 position occurs.

Scheme 45



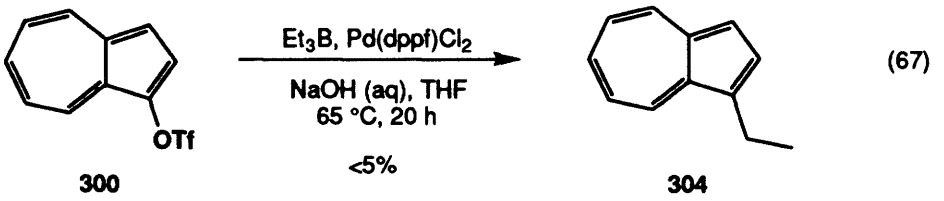
302 **303**

Cross Coupling Reactions of Azulene Triflates

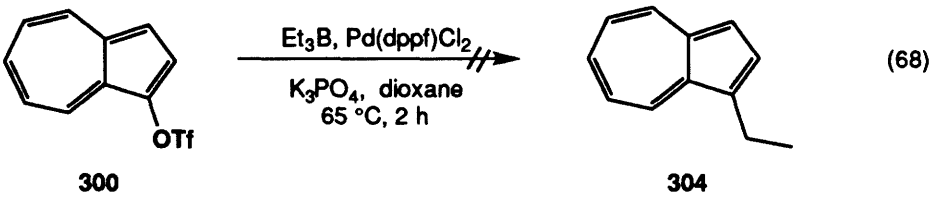
With a convenient method available for the synthesis of the desired azulene triflates, we turned our attention towards an examination of their reactivity in various cross coupling reactions. Among the first protocols examined was the Suzuki reaction with triethylborane (eq 67).[ref] Initial experiments utilizing the procedure originally

[141]Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.

designed for the coupling of aryl halides with trialkylboranes were not successful. Treatment of **300** with excess triethylborane in the presence of a catalytic amount of [1,1'-bis(diphenylphosphino)ferrocenyl]palladium(II) chloride and 3 equiv of aqueous sodium hydroxide led to the formation of 1-ethylazulene (**304**)[142] in very low yield. TLC analysis of this reaction indicated that the majority of **300** was hydrolyzed to 1-hydroxyazulene, which subsequently decomposed. Interestingly, under these same conditions, the triflate derivative of 1-naphthol reacts with triethylborane to give 1-ethylnaphthalene in 85% yield. Coupling under anhydrous conditions with thallium carbonate or sodium methoxide as the base did not improve the yield of **304**. Surprisingly, employing the conditions developed exclusively for the coupling of aryl triflates with organoboranes[143] (potassium phosphate as the base, dioxane as the solvent) did not lead to any of the desired product (eq 68). Instead, decomposition of the azulene triflate[144] via hydrolysis to 1-hydroxyazulene appeared to be the course of each of these reactions.



(67)



(68)

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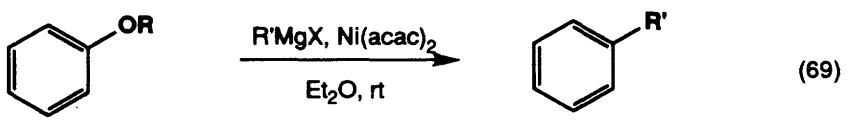
[142]For a previous synthesis of **304**, see: Anderson, A. G.; Breazeale, R. D. *J. Org. Chem.* **1969**, *34*, 2375.
[143](a)Oh-e, T.; Miyaura, N.; Suzuki, A. *Synlett* **1990**, 221. For other examples of coupling reactions of aryl triflates with organoboranes, see (b) Fu, J.; Snieckus, V. *Tetrahedron Lett.* **1990**, *31*, 1665. (c) Shieh, W. -C.; Carlson, J. A. *J. Org. Chem.* **1992**, *57*, 379. (d) Huth, A.; Beetz, I.; Schumann, I. *Tetrahedron* **1989**, *45*, 6679.
[144]Stille has previously described the decompostion of aryl triflates in polar aprotic media. See: Eschavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478, and references cited therein.

These disappointing results led us to examine the stability of **300** in the various solvents typically employed for cross coupling reactions. At 25 °C in polar aprotic solvents such as *N*-methylpyrrolidinone, the azulene triflate is readily degraded to the corresponding 1-hydroxyazulene, even with rigorous degassing of the solution or in the presence of BHT. Presumably, this decomposition is occurring by a transfer of the triflate group from the azulene substrate to the solvent. However, **300** does not exhibit any remarkable instability in less polar media such as tetrahydrofuran or diethyl ether.

In 1992, Snieckus and coworkers described the nickel-catalyzed cross coupling reaction of various Grignard reagents with aryl triflates and carbamates (eq 69).[145] This protocol seemed to offer the conditions we thought necessary to maximize the cross coupling of **300**: a fast reaction at low temperatures and a solvent in which our substrate is stable. As illustrated in eq 70, treatment of **300** with ethylmagnesium bromide in the presence of $Ni(acac)_2$ furnished a 7:1 ratio of 1-ethylazulene (**304**) and azulene (**28**) (the β-hydride elimination product) in low overall yield. The analogous reaction with methylmagnesium bromide (in which β-hydride elimination is not possible) provided 1-methylazulene (**307**)[146] with little increase in yield over the previous case (eq 71). Regardless of the Grignard reagent employed, significant decomposition of the starting material is observed under these conditions.

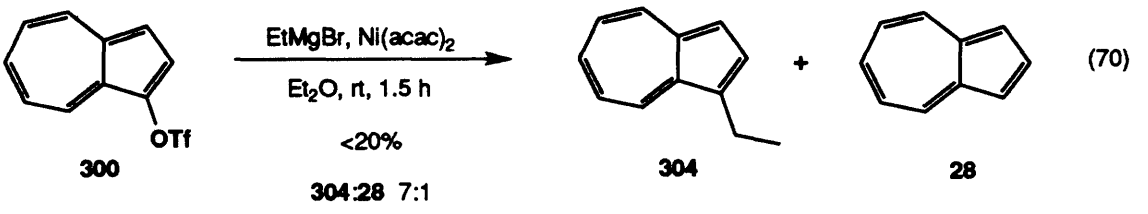


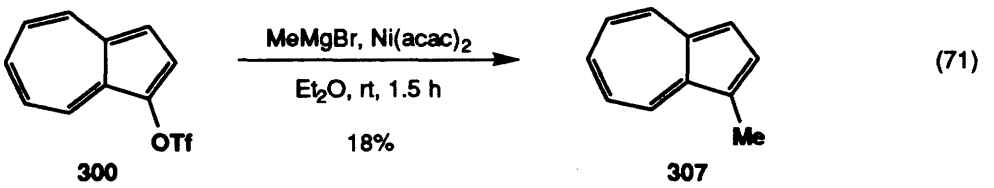
(69)

R = SO_2CF_3, **305a**
R = $CONEt_2$, **305b**

306

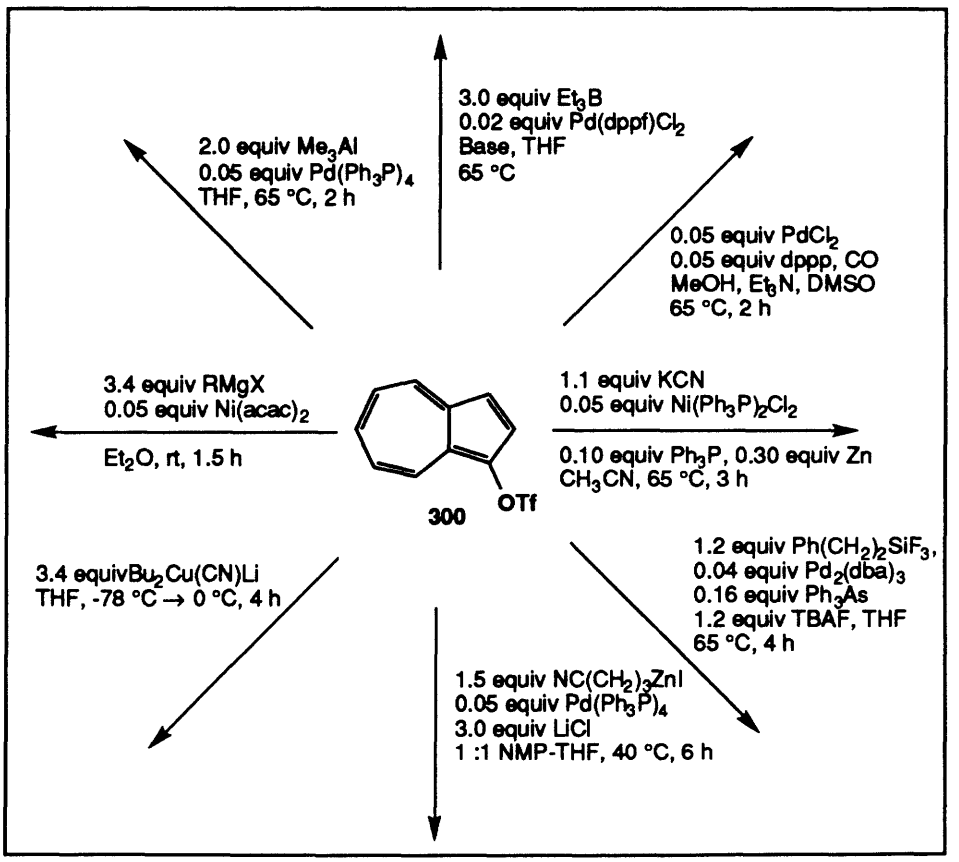
[145]Sengupta, S.; Leite, M.; Raslan, D. S.; Quesnelle, C.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 4066.
[146]Hafner, K. *Liebigs Ann. Chem.* **1957**, *606*, 79.





As indicated in Scheme 46, similar results were obtained by treatment of **300** under other coupling protocols.

Scheme 46



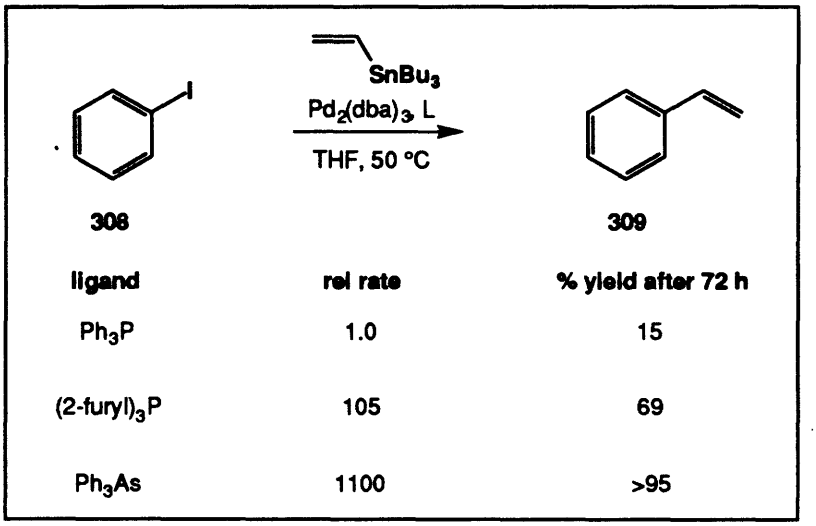
Reaction of **300** with organozinc halides,[136] $Bu_2Cu(CN)Li$,[147] organoaluminum reagents,[148] alkyltrifluorosilanes,[149] inorganic cyanides,[150] and carbon monoxide[151] produced, at best, traces of the desired coupled products. In all examples, decomposition of the starting material was the predominant path of these reactions. We did not choose to examine the classical Stille reaction with organostannanes[152] since our substrate is unstable to the conditions normally employed for this procedure. A recent modification of this protocol, however, has proven to be the best method currently available for the coupling of the azulene triflate **300**.

In 1990, Farina and coworkers reported the development of a variant of the classic Stille reaction in which dramatic rate increases are possible.[153] These researchers found that the rate of coupling is significantly affected by the choice of the catalyst system (Scheme 47). The use of ligands which strongly complex palladium, such as triphenylphosphine, leads to a much slower reaction compared to weakly coordinating ligands, such as triphenylarsine or tris-(2-furyl)phosphine. This effect can be traced to a key ligand dissociation just prior to the rate determining transmetallation step of the catalytic cycle.[154] Ligands which dissociate more readily from palladium allow the transmetallation step to occur faster, and thus the overall rate of the coupling reaction is increased. For reactions of substrates that are unstable to the classic Stille conditions, Farina observed that this modified version is an effective alternative.

---

[147]Mc Murray, J. E.; Mohanraj, S. *Tetrahedron Lett.* **1983**, *24*, 2723.
[148]Hirota, K.; Isobe, Y.; Maki, Y. *J. Chem. Soc. Perkin Trans. I* **1989**, 2513.
[149](a) Hatanaka, Y.; Fukushima, S.; Hiyama, T. *Tetrahedron* **1992**, *48*, 2113. (b) Hatanaka, Y.; Hiyama, T. *Synlett* **1991**, 845. (c) Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* **1990**, *31*, 2719. (d) Hosomi, A.; Kohra, S.; Tominaga, Y. *Chem. Pharm. Bull.* **1988**, *36*, 4622.
[150]Chamber, M. R. I.; Widdowson, D. A. *J. Chem. Soc. Perkin Trans. I* **1989**, 1365.
[151]Gerlach, U.; Wollmann, T. *Tetrahedron Lett.* **1992**, *33*, 5499.
[152]For general reviews of the Stille reaction, see: (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Mitchell, T. N. *Synthesis* **1992**, 803.
[153]Farina, V.; Baker, S. R.; Benigni, D. A.; Hauck, S. I.; Sapino, C. *J. Org. Chem.* **1990**, *55*, 5833.
[154]For a more detailed explanation of the role triphenylarsine and tris-(2-furyl)phosphine play in accelerating this reaction, see (a) Farina, V. Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585 and references cited therein. (b) Farina, V.; Roth, G. P. manuscript in press.

Scheme 47

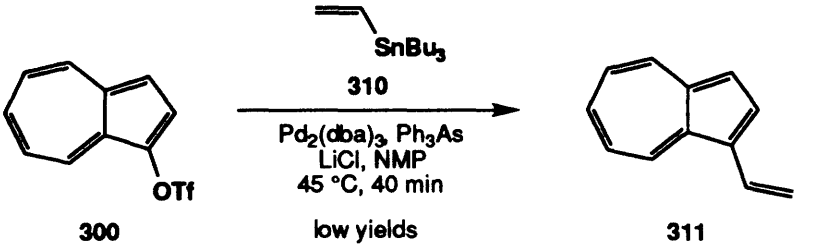


308 **309**

ligand	rel rate	% yield after 72 h
Ph_3P	1.0	15
$(2\text{-furyl})_3P$	105	69
Ph_3As	1100	>95

The mild conditions and short reaction times of the Farina conditions suggested to us that it might be useful for the coupling of azulene triflates. Since the dramatic rate increases are seen only for unsaturated stannanes, we chose to examine the reaction of **300** with tributylvinylstannane (**310**). As outlined in eq 72, treatment of **300** with **310** in the presence of 0.04 equiv of tris(dibenzylideneacetone)dipalladium (an air-stable source of Pd(0)) and 0.16 equiv of triphenylarsine leads to a rapid conversion of the starting material to 1-vinylazulene (**311**),[155] an unstable blue oil. While we were initially excited about this result, the difficulties encountered in handling **311** led us to focus our attention on similar coupling reactions which would provide more stable products. Attempts to introduced an acetlyene moiety by the cross coupling reaction of **300** with (phenylethynyl)tributylstannane under Farina's conditions (0.04 equiv of $Pd_2(dba)_3$, 0.16 equiv of Ph_3As, 3.0 equiv of LiCl, NMP, 40 °C, 18 h) led strictly to decomposition of the starting material.

[155]1-Vinylazulene has previously been reported to be extremely sensitive to air and undergoes rapid polymerization upon standing. See: McDonald, R. N.; Stewart, W. S. *J. Org. Chem.* **1965**, *30*, 270. We found that this material also decomposed during attempted purification on silica gel or neutral alumina.



(72)

However, the reaction of **300** with 1-ethoxy-1-(trimethylstannyl)ethylene (**312**)[156] occurred readily, providing 1-acetylazulene (**313**)[157] as a purple oil after acidic workup (eq 73). A considerable amount of effort was expended in determining the optimal conditions for this transformation. For this case, triphenylarsine proved to be the superior ligand, although tris(2-furyl)phosphine did support the reaction. Conducting this reaction under the "ligandless" conditions of Beletskaya[158] did not lead to a successful transformation of **300** to **313**. The addition of a co-catalyst such as copper(I) iodide[159] had no significant effect on the reaction, although we determined that the inclusion of excess lithium chloride was necessary for the success of the reaction. Unfortunately, this reaction requires the polar solvent *N*-methylpyrrolidinone, as **300** is recovered unchanged when this coupling procedure is conducted in tetrahydrofuran. In accordance with our earlier observations, a significant amount of **300** is lost during the reaction due to decomposition of the starting material. However, unlike most of the previous examples, Farina's conditions make the cross coupling competitive with decomposition.

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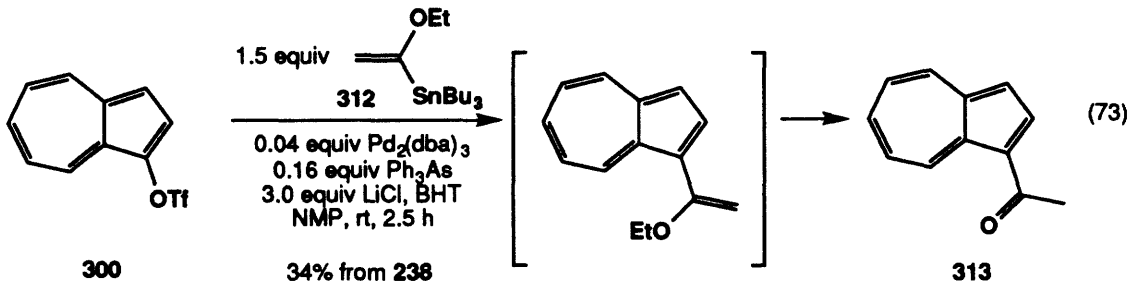
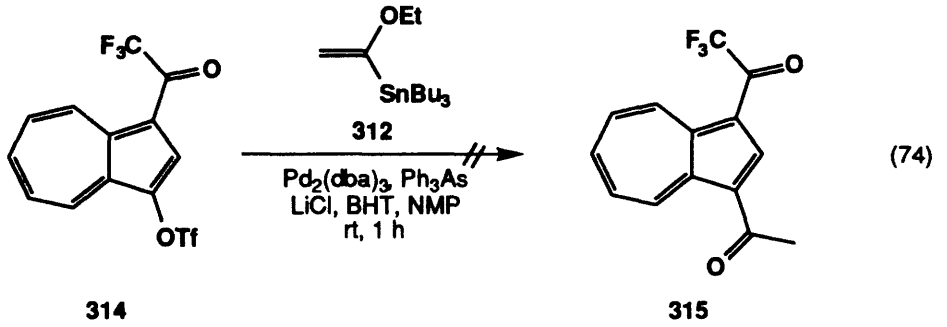
[156]Kwon, H. B.; McKee, B. H.; Stille, J. K. *J. Org. Chem.* **1980**, *55*, 3114.
[157]For a previous synthesis of **313**, see ref. 142.
[158]Beletskaya, I. P. *Organomet. Chem.* **1983**, *250*, 551.
[159]For examples of co-catalysis by copper(I) salts, see: (a) Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359. (b) Gomez-Bengoa, E.; Echavarren, A. M. *J. Org. Chem.* **1991**, *56*, 3497. (c) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W. *Tetrahedron Lett.* **1992**, *33*, 919. (d) Liebeskind, L. S.; Riesinger, S. W. *J. Org. Chem.* **1993**, *58*, 408.



(73)

We believe that the incorporation of electron withdrawing functionalities at the C-3 position may help to increase the rate of the coupling reaction even more, as Horino's work has demonstrated (*vide supra*). However, initial attempts to accomplish this with the azulene triflate derivative **314**[160] using the Farina conditions led to decomposition of the starting material (eq 74).

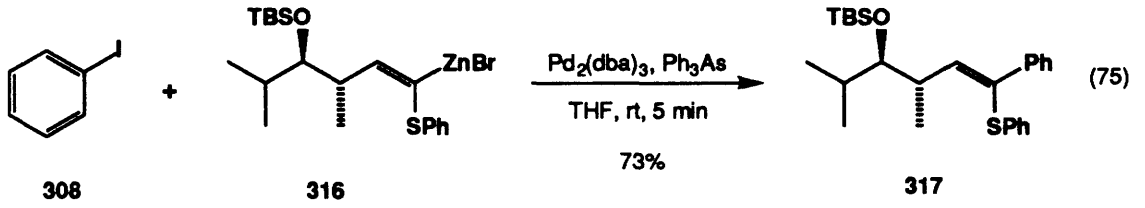


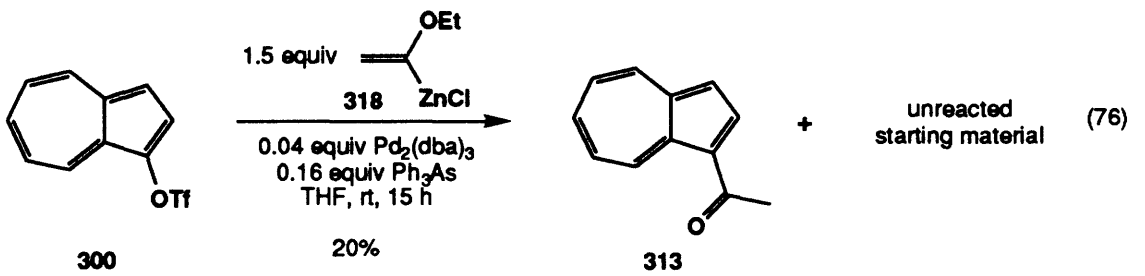
(74)

The application of Farina's catalyst system to other transition metal-mediated cross coupling reactions has already begun to appear. For instance, we found that the coupling reactions of 1-acetoxy-4-iodoazulene with organozinc halides described above (see pp 105) occurr very rapidly with the Pd_2dba_3-triphenylarsine catalyst system. Kocienski and coworkers noticed a similar effect in the coupling of α-(phenylthio)alkenylzinc reagents with various organic electrophiles as shown in eq 75.[161] This report led us to consider the reaction of azulene triflate **300** with the alkenylzinc

[160]This compound was synthesized by reaction of **300** with trifluoroacetic anhydride according to the procedure of Anderson. See: Anderson, A. G., Jr.; Anderson, R. G. *J. Org. Chem.* **1962**, *27*, 3578.
[161]Pimm, A.; Kocienski, P.; Street, S. D. A. *Synlett* **1992**, 886.

halide **318**[162] (eq 76). We were pleased to find that the coupling reaction did occur, although the process was rather slow. More importantly, **300** appeared to be stable under these reaction conditions, with minimal decomposition of the starting material after 15 h at room temperature. Further study of this system may lead to a reaction that is even more effective than the corresponding tin-based process.





It is clear from the results of the various cross coupling reactions of **300** that azulene triflates do not behave as "ordinary" aryl triflates. While this fact is rather disappointing, we have demonstrated that under proper conditions, these triflates will undergo useful cross coupling reactions. Further study of these unusual triflate derivatives should lead to a broader understanding of their nature and the requirements for successful coupling reactions.

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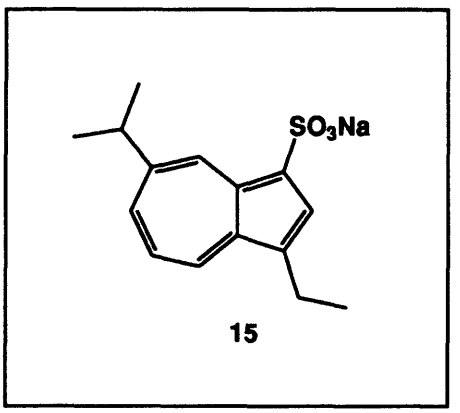
[162]For examples of coupling reactions with this reagent, see: (a) Russell, C. E.; Hegedus, L. S. *J. Am. Chem. Soc.* **1983**, *105*, 943. (b) Negishi, E.; Luo, F. -T. J. *J. Org. Chem.* **1983**, *48*, 1560.

The Synthesis of *Azuletil Sodium*

In large part, the true measure of the utility of a new method depends upon its applicability to relevant target molecules. As mentioned in Chapter 1, there are a wide variety of commercially interesting azulene derivatives which could serve as suitable test cases for our new method. We have chosen to focus our attention on the anti-ulcerative drug *Azuletil sodium* (**15**) (Figure 3). Before describing our synthesis of this compound, however, a digression to discuss this interesting class of ulcer medications is appropriate.

Figure 3



15

Azulenesulfonic acid derivatives have been used as anti-ulcerative agents for a number of years. Shown below are two derivatives, sodium guaiazulene-3-sulfonate (**14**)[163] and sodium azulene-1-sulfonate (**319**),[164] which have been widely prescribed in Japan for the treatment of certain peptic ulcers. Because both of these drugs have proven to be relatively unstable towards light and heat, researchers at the Kotobuki Seiyaku Company have been interested in developing replacements for these compounds.

Scheme 48

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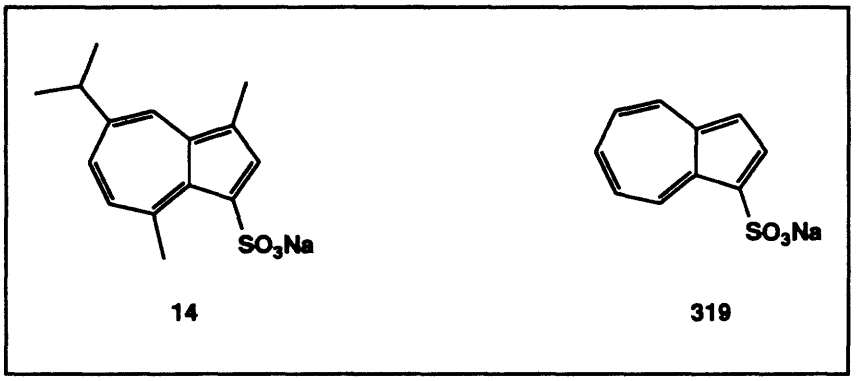
[163]Okabe, S.; Takeuchi, K.; Honda, K.; Takagi, K. *Pharmacometrics* **1975**, *9*, 31.

[164]This compound has been patented under the trade name Azusalen by the Otha Pharamceutical Company. See: *The Merck Index*, Tenth Ed.; Merck And Co.: Rahway, NJ, 1983, p 939.



14 319

In 1988, Yanagisawa and colleagues at the Kotobuki Company developed a new azulenesulfonic acid derivative **15** which demonstrated more potent pepsin inhibitory properties and greater stability than both **14** and **319**.[165] Extensive structure-activity relationship studies concluded that although a wide variety of azulenesulfonic acids possessed anti-ulcerative properties, **15** was by far the most potent derivative.[166] The synthesis of **15** is outlined below in Scheme 49. The 5-isopropyl tropolone derivative **320** is converted to the corresponding tosylate in quantitiative yield by exposure to *p*-toluenesulfonyl chloride and pyridine in dichloromethane.[167] Reaction of this tosylate derivative with dimethyl malonate and sodium methoxide provides the cyclohepta[b]furan-2-one **321**. Although not specified, Yanagisawa reports "good yields" for this conversion. Treatment of **321** with the morpholino enamine of butyraldehyde provides azulene derivative **322** in "greater than 90% yield" via a previously described [8+2] cycloaddition strategy (*vide supra*). Decarboxylation of **322** with phosphoric acid furnishes in "good yield" 1-ethyl-5-isopropylazulene (**323**) which undergoes electrophilic sulfonylation with SO_3·pyridine complex in 90% yield to provide **15** as a blue solid. The

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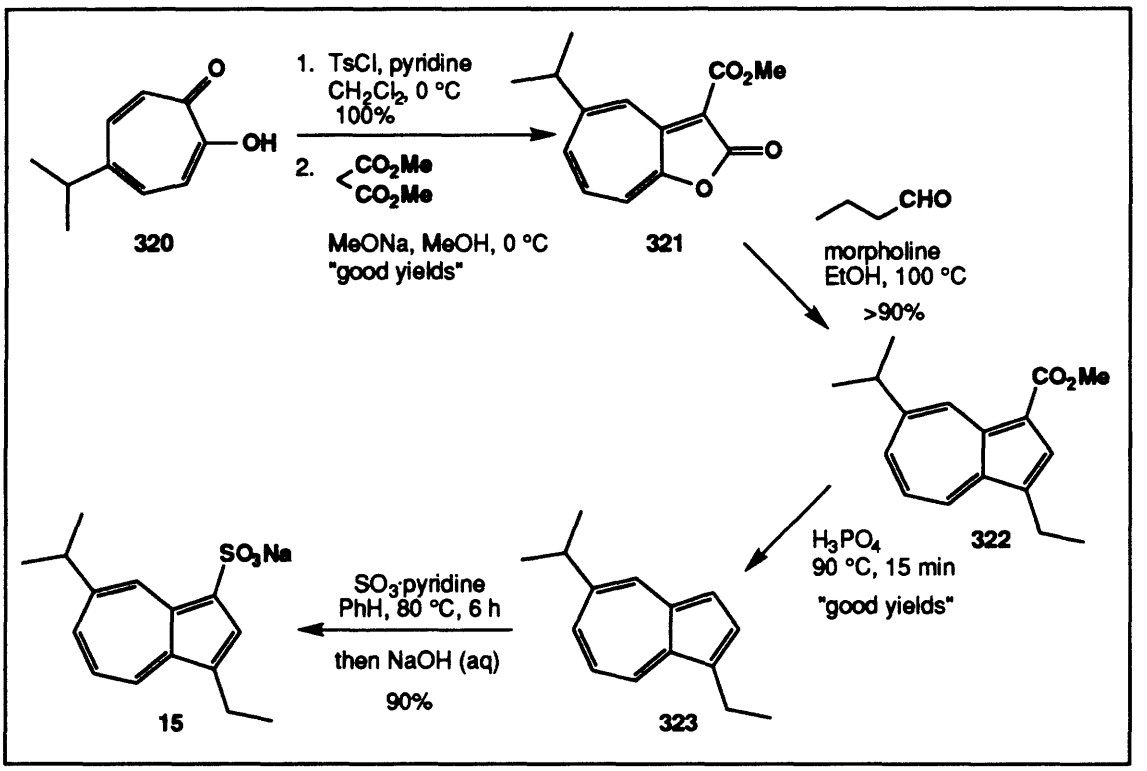
[165]Yanagisawa, T.; Wakabayashi, S.; Tomiyama, T.; Yasunami, M.; Takase, K. *Chem. Pharm. Bull.* **1988**, *36*, 641.

[166](a) Yanagisawa, T.; Kosakai, K.; Tomiyama, T.; Yasunami, M.; Takase, K. *Chem. Pharm. Bull.* **1990**, *38*, 3355. (b) Yanagisawa, T.; Kosakai, K.; Izawa, C.; Tomiyama, T.; Yasunami, M. *Chem. Pharm. Bull.* **1991**, *39*, 2429. (c) For the synthesis of related bismuth-containing anti-ulceratives, see: Tomiyama, T.; Tomiyama, I.; Yanagisawa, T.; Kosakai, K. *Jpn. Kokai Tokkyo Koho JP 02,282,392 [90,282,392] CA* **1991**, 115:70993t.

[167]Nozoe, T.; Imafuku, K.; Yin, B. -Z.; Honda, M.; Goto, Y.; Hara, Y.; Andoh, T.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2531.

major drawback to this strategy is its reliance on the substituted tropolone derivative **320**. As discussed in Chapter 1, the synthesis of these compounds generally requires several steps.

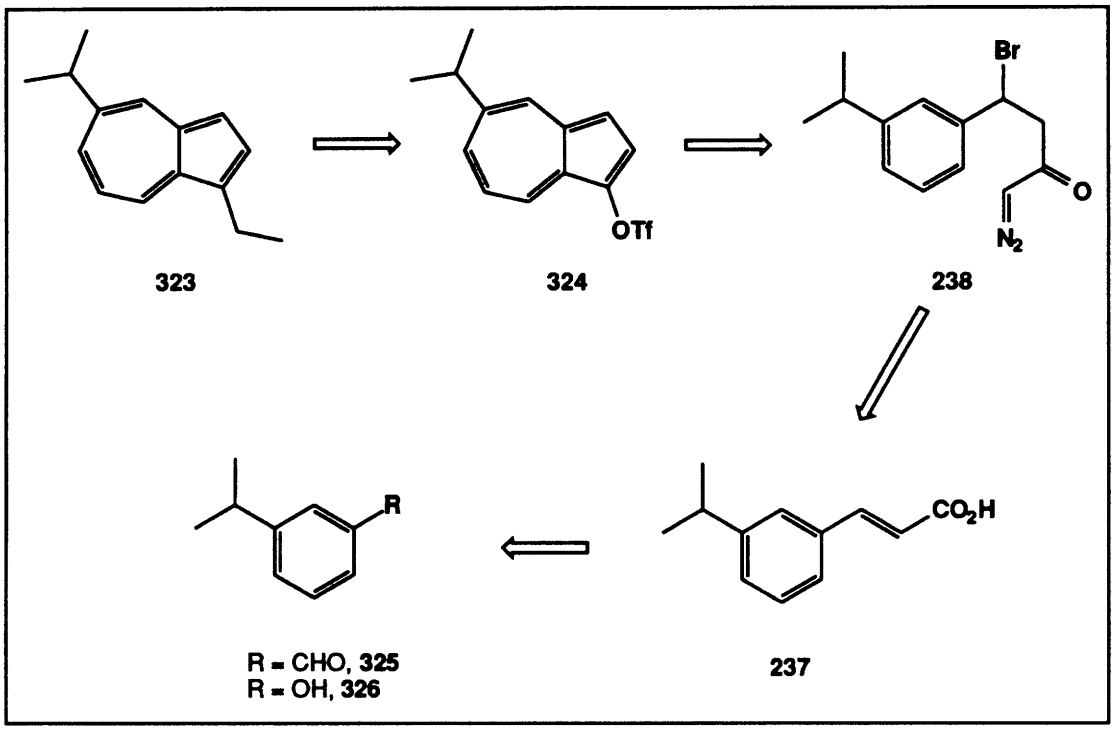
Scheme 49



We believed that our new ring expansion-annulation strategy could be applied to provide a more efficient synthesis of *Azuletil sodium*. As outlined below (Scheme 50) 1-ethyl-5-isopropylazulene (**323**) would arise from a cross coupling reaction involving the 5-isopropylazulene triflate derivative **324**. The ring expansion-annulation reaction of the β-bromo diazo ketone **238**, as previously discussed in Chapter 3, provides the requisite 1-hydroxyazulene derivative with the proper regiochemistry. The diazo ketone intermediate **238** would be prepared from 3-isopropylcinnamic acid (**237**), which in turn should be available in short order from either 3-isopropylbenzaldehyde (**325**) or 3-isopropylphenol (**326**).

Unfortunately, the aldehyde **325** is not commercially available. Gilman has previously described the preparation of this material via a low yield Friedel-Crafts reaction of benzaldehyde with 2-chloropropane.[168] Although this approach could probably be optimized and might be convenient for the large scale production of **325**,

Scheme 50



we chose instead to produce this aldehyde via a formylation reaction of an appropriate aryllithium species. Thus, metal-halogen exchange reaction of **327**[169] with *n*-BuLi at -78 °C followed by quenching with *N,N*-dimethylformamide provided **325** in 87% yield (Scheme 51). Subsequently, we found that the crude aldehyde could be carried on to the next reaction with no ill effect on the yield. In fact, the entire sequence from the bromide **327** to the diazo ketone **238** could be performed without purification of any of the intermediates. Thus, as previously discussed in Chapter 3, application of the Knoevangel

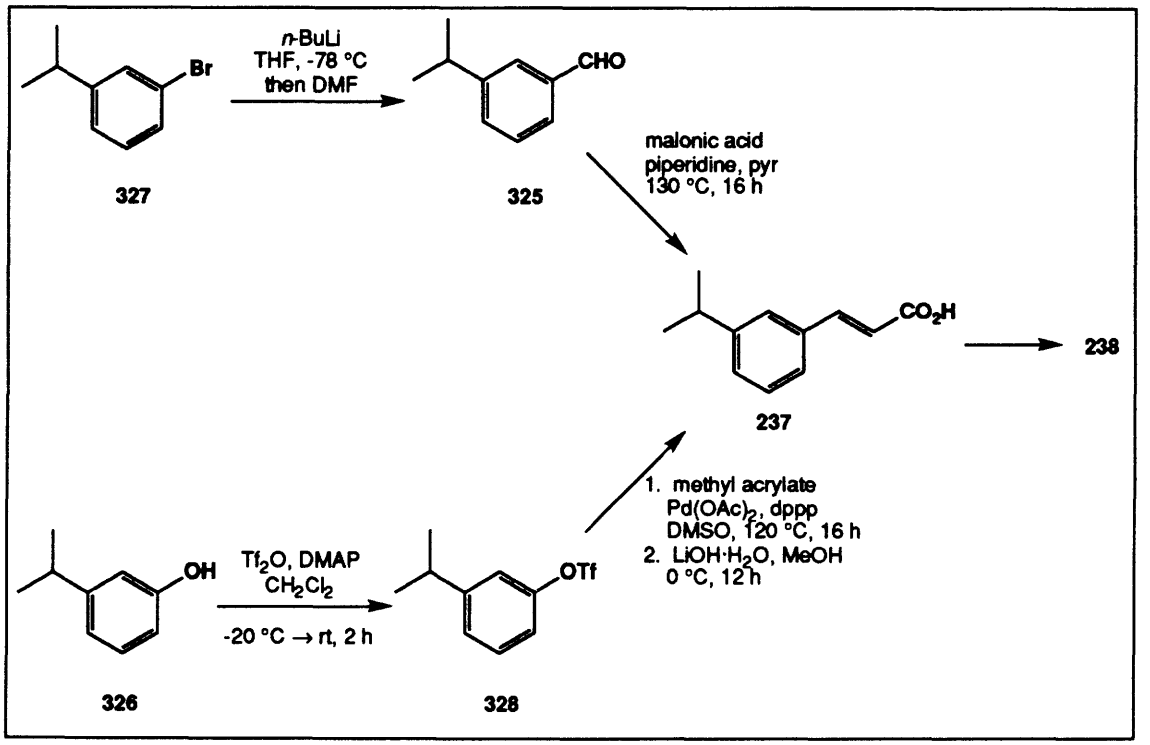
[168]Gilman, H.; Burtner, R. R. *J. Am. Chem. Soc.* **1935**, *57*, 909.

[169]Ths compound was prepared in our laboratory by Hiroo Koyama by the reaction of 3-bromobenzaldehyde with Me_2TiCl_2, according to the method of Reetz. See Reetz, M. T.; Kyung, S. -H. *Chem. Ber.* **1987**, *120*, 123.

reaction conditions described by Koo and coworkers (2 equiv of malonic acid, 2 equiv of piperidine, 130 °C, 16 h)[170] to **325** furnished 3-isopropylcinnamic acid (**237**) as a white solid.

An alternative route to this acid was developed based on 3-isopropylphenol (**326**). The reaction of this commercially available phenol with 1. 2 equiv of triflic anhydride and 4-dimethylaminopyridine in dichloromethane at -20 °C provided the triflate derivative **328** in 97% yield. Once again, no purification of this or any other intermediate to diazo ketone **238** was necessary. Heck coupling[171] of **328** with methyl acrylate in the presence of 0.1 equiv of palladium(II) acetate and 0.1 equiv 1,3-bis(diphenylphosphino)propane (dimethylsulfoxide, 120 °C, 16 h), followed by ester hydrolysis with excess lithium hydroxide afforded **237**.

Scheme 51



[170]Koo, J.; Fish, M. S.; Walker, G. N.; Blake, R. *Org. Synth. Coll. Vol. 4*, **1963**, 327.
[171]Heck reactions with aryl triflates are well known. For some recent examples, see: (a) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *Synlett* **1992**, 871. (b) Cabri, W.; Candiani, I.; DeBernardinis, S.; Francalanci, F.; Penco, S. *J. Org. Chem.* **1991**, *56*, 5796.

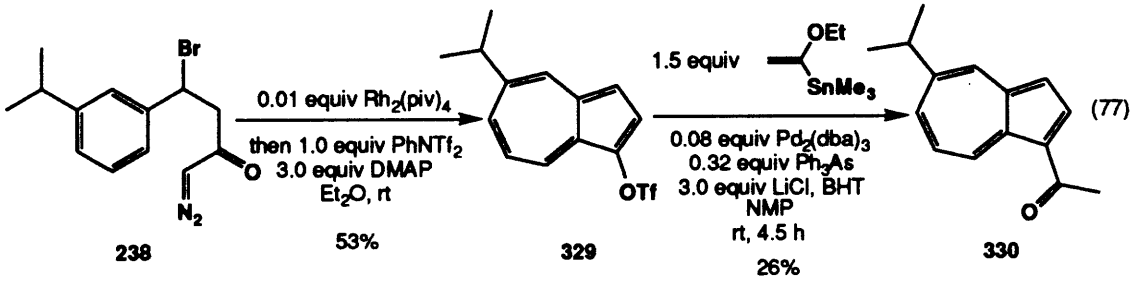
As previously described in Chapter 3, the synthesis of the requisite β-bromo diazo ketone **238** is accomplished by hydrobromination of **237**, followed by reaction with oxalyl chloride and diazomethane. After flash chromatography of the crude product, **238** is isolated as a yellow oil in 50-60% overall yield from either **325** or **327**.

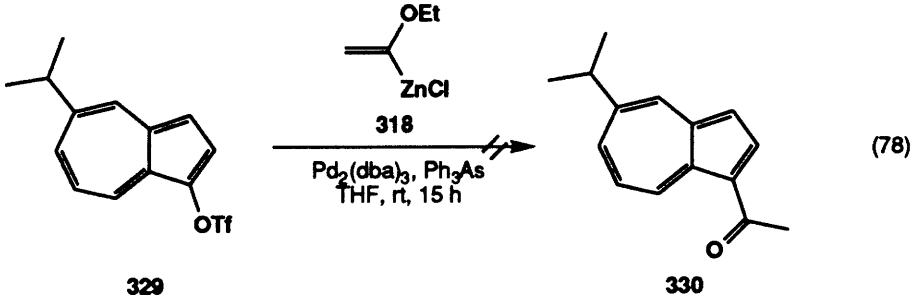
As shown in eq 77, the 5-isopropylazulene triflate derivative **329** is produced in a similar manner to the unsubstituted azulene triflate **300**; however, the ring expansion-annulation reaction of diazo ketone **238**, as discussed in the preceding chapter, must be performed in diethyl ether. This reaction provided the desired azulene triflate derivative **329** as a blue oil, which was purified by flash chromatography and used immediately in next reaction. Although not determined, it is reasonable to assume that the yield of this reaction is similar to the 53% yield obtained when acetic anhydride is employed as the trapping reagent.

Based on our previous results with the unsubstituted azulene triflate **300**, it seemed that direct conversion of **329** to the desired 1-ethyl-5-isopropylazulene (**323**) by a transition metal-mediated coupling reaction with an appropriate ethyl-substituted metal partner would not be successful. A two step conversion of **329** to **323** by coupling with a vinyl- or ethynyl-substituted metal derivative followed by hydrogenation appeared equally improbable (*vide supra*). On the other hand, a two step process involving conversion of **329** to the corresponding 1-acetyl derivative followed by reduction to **323** seemed to offer the best chance for success.

We have shown that the unsubstituted azulene triflate **300** can be converted to 1-acetylazulene (**313**) in 53% yield by coupling with 1-ethoxy-1-(trimethylstannyl)ethylene under Farina's conditions (*vide supra*). Initial attempts to apply this coupling procedure to the 5-isopropyl-substituted azulene triflate **329** demonstrated that this material undergoes a slower reaction than **300**; therefore, more catalyst was employed. Thus, treatment of **329** with 1.5 equiv of 1-ethoxy-1-(trimethylstannyl)ethylene in the presence of 0.08 equiv of $Pd_2(dba)_3$, 0.32 equiv of Ph_3As, and 3.0 equiv of LiCl (NMP, rt, 4.5 h)

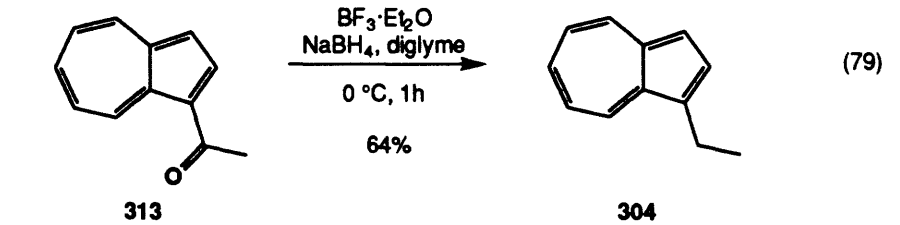
provided a crude brown oil. Flash chromatography of this material furnished 1-acetyl-5-isopropylazulene (**330**) as a purple solid in 14% overall yield from diazo ketone **238**. The ^{1}H and ^{13}C NMR spectra (as well as IR and UV-vis data) for this compound were fully consistent with the desired structure. Curiously, the reaction of **329** with the corresponding organozinc species led only to the recovery of unchanged starting material, although the reasons for this are unknown (eq 78).



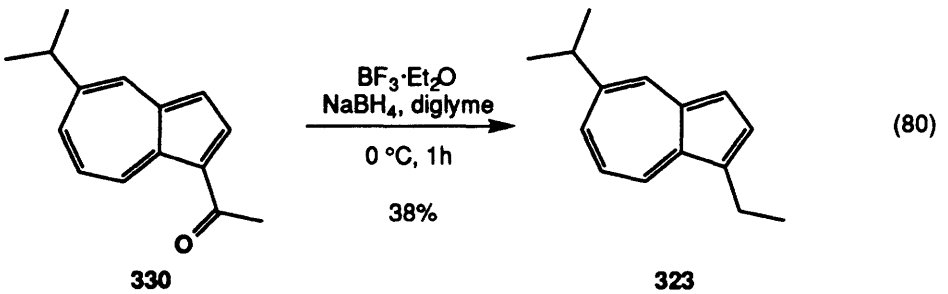


Our synthesis of *Azuletil sodium* next requires conversion of **330** to the penultimate intermediate in the Kotobuki Seiyaku route, 1-ethyl-5-isopropylazulene (**323**). Anderson and Breazeale had previously reported that various acetylated azulene derivatives could be reduced to the corresponding methylene compound by reaction with diborane.[142] For example, the reduction of 1-acetylazulene (**313**) with diborane (generated *in situ* from boron trifluoride etherate and sodium borohydride) gives 1-ethylazulene (**304**) in 64% yield (eq 79). The analogous reduction of 1-acetyl-5-isopropylazulene is shown in eq 80. Addition of excess boron trifluoride etherate to **330** resulted in the formation of an orange Lewis acid complex. This suspension was then

added dropwise over 15 min to excess sodium borohydride in diglyme (an immediate color change from orange to blue was noted as each drop was added). Standard workup and flash chromatography provided 1-ethyl-5-isopropylazulene (**330**) as a blue oil in 38% yield. Yanagisawa and coworkers have previously demonstrated that this intermediate can be converted to *Azuletil sodium* by electrophilic sulfonylation with SO_3·pyridine complex in 90% yield. Presently, none of the steps of our synthesis of *Azuletil sodium* have been rigorously optimized, making a comparison of the overall yields of the two routes misleading. However, our synthesis of this compound does allow us to demonstrate that the second argument of our original hypothesis is valid: azulene triflates can be used as intermediates for the construction of other substituted azulene derivatives.



313 304 (79)



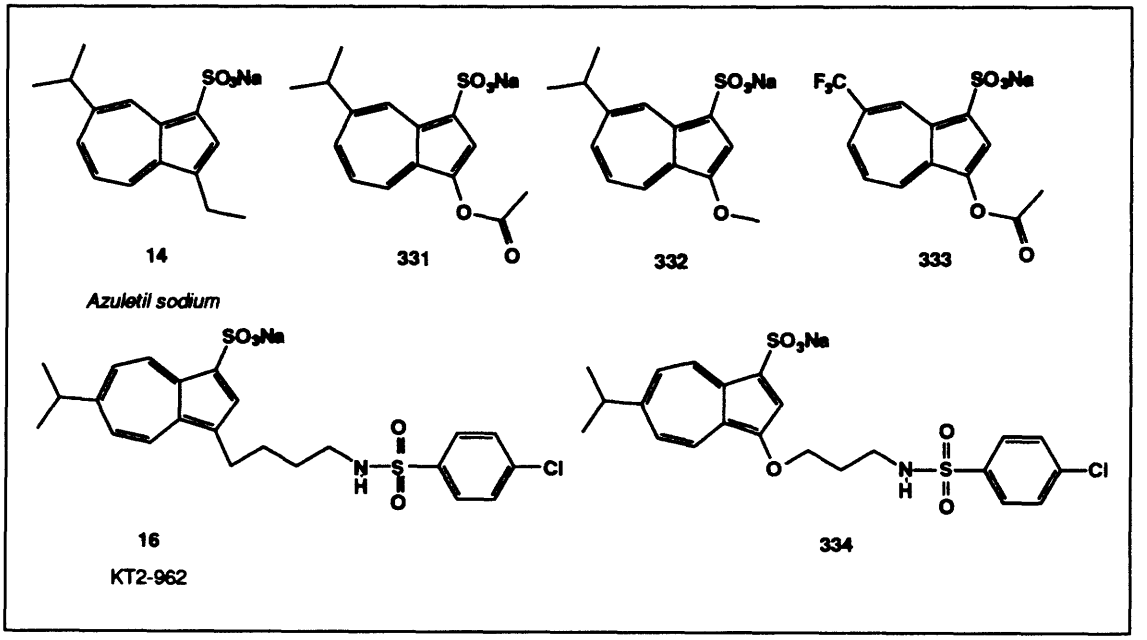
330 323 (80)

Future Applications of 1-Hydroxyazulene Derivatives

The biological activity of the novel 1-hydroxyazulene derivatives which are readily available via our new ring expansion-annulation strategy is currently unknown. Recently, we have become interested in determining whether certain 1-hydroxyazulene

derivatives are themselves biologically active compounds. Towards this end, we have begun to synthesize structural analogs of several of certain biologically active azulenes under investigation at the Kotobuki Seiyaku Company. Several of our initial targets are 1-hydroxyazulenes which are structurally related to *Azuletil sodium* (Scheme 52).

Scheme 52



For example, we are in the process of synthesizing azulene derivatives such as **331**, **332**, and **333**.[172] In addition, analogs of Kotobuki's potent thromboxane A_2 receptor antagonist KT2-962 (**16**, see pp 17), such as **334**, are also being prepared. The future direction of this ongoing azulene project is largely dependent upon the results of the biological screening of these three analogs.

[172]The author is greatly indebted to Adam Renslo for assistance in the synthesis of **331** and **332** and to Melanie Bartow for work on the synthesis of **333**.

Part II

Synthetic Approaches to Salvilenone

CHAPTER 1

Introduction and Background

Isolation and Structure Determination of Salvilenone

The traditional Chinese medicinal herb *Salvia miltiorrhiza* has been commonly prescribed for a number of blood-related disease states including hemorrhages, menstrual disorders, and miscarriages.[173,174] Examination of the individual chemical components of this plant's dried roots (commonly referred to as Dan Shen) revealed an extensive number of naphthaquinone and phenanthraquinone diterpenes. In 1985, during a study of some of the minor components of Dan Shen extracts, Hayashi and coworkers isolated a bright yellow pigment with properties quite different from the previously isolated quinone derivatives.[175] Through the use of sophisticated heteronuclear NMR experiments, these researchers were able to deduce the structure of this yellow material which they subsequently named salvilenone (**335**) (Figure 4). This interesting phenalenone had previously been reported by Eugster a decade earlier when these researchers determined that treatment of various naturally-occurring royleanones with mineral acid led to the formation of **335**.[176] In contrast, Hayashi's isolation of this material was conducted under

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[173]For a recent review of Chinese traditional medicine, see: Liang, H.; Jin, Z. In *Comprehensive Medicinal Chemistry*; Hansch, C.; Sammes, P. G.; Taylor, J. B., Eds.; Pergamon Press: Oxford, 1990, Vol. 1, pp 99-111.

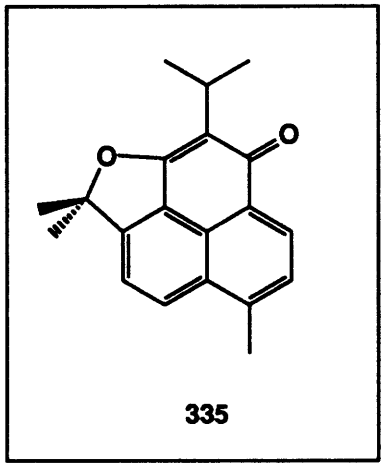
[174](a) Chien, M. K.; Young, P. T.; Ku, W. H.; Chen, Z. X.; Chen, H. T.; Yeh, H. C. *Acta Chim. Sinica* **1978**, *36*, 199. (b) Wang, Y. P.; Chen, Y. H.; Xu, D. Z.; Jiang, J. X. *Shang-hai Ti 1 I Hsueh Yuan Hseuh Pao* **1980**, *7*, 347. (c) Luo, H.; Wu, B.; Yong, Z.; Jin, Y. *Acta Pharm. Sinica* **1985**, *20*, 542. (d) Zhou, Q. in *Advances in Chinese Materials Research*; Chang, H. M.; Yeung, H. W.; Tso, W. W.; Koo, H., Eds.; World Scientific Publishing: Singapore, 1985, p 215. (e) Zhou, C. W.; Li, D. Y.; Gen, W. C.; Sheng, T. G. *Acta Pharm. Sinica* **1979**, *37*, 277.

[175]Kusumi, T.; Ooi, T.; Hayashi, T.; Kakisawa, H. *Phytochemistry* **1985**, *24*, 2118.

[176]Hensch, M.; Eugster, C. H.; Weber, H. -P. *Helv. Chim. Acta* **1975**, *58*, 1934.

neutral conditions, thus leading to the conclusion that salvilenone is indeed a naturally occurring compound and not simply an artifact of the isolation procedure.

Figure 4



335

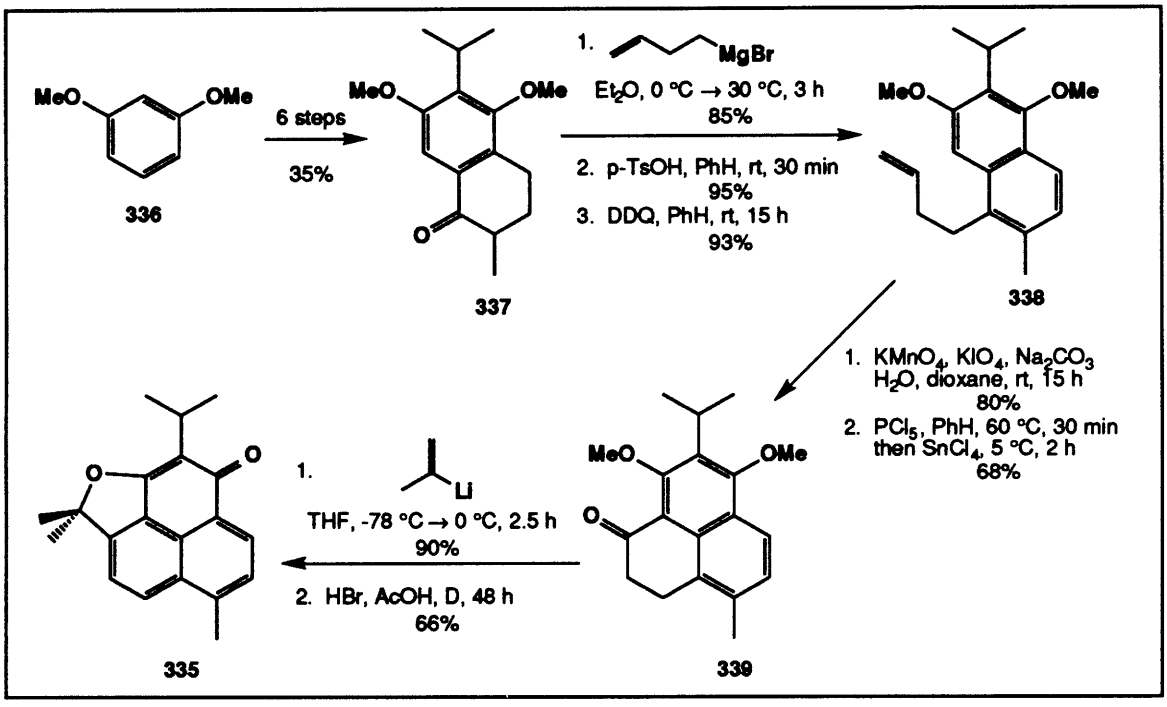
Previous Total Syntheses of Salvilenone

Since Hayashi's initial disclosure, two total syntheses of salvilenone have been reported. In 1988, Kakisawa and coworkers published the first total synthesis of this compound;[177] their route to **335** is shown below in Scheme 53. Construction of the tetralone derivative **337** was accomplished in six steps from resorcinol dimethyl ether (**336**) via traditional aromatic substitution procedures. The third ring of the phenalene system was installed by addition of 3-butenylmagnesium bromide to **337**, followed by dehydration of the resulting alcohol and oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone. Oxidative cleavage of the terminal olefin of **338** to give a carboxylic acid, acid chloride formation, and ring closure via Friedel-Crafts acylation provided dihydrophenalenone derivative **339**. The synthesis of salvilenone was completed by the addition of isopropenyllithium to the carbonyl group of **339** and treatment of the

[177](a) Zheng, G. -C.; Kojima, T.; Kakisawa, H. *Heterocycles* **1988**, *27*, 1341. (b) Zheng, G. -C.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1117.

resulting tertiary alcohol derivative with acid. This 14 step sequence proceeds in 8.5% overall yield, a respectable result considering the linear nature of this strategy. As a whole, however, linear approaches of this type are considerably less attractive than convergent ones.

Scheme 53



Recently, the second total synthesis of salvilenone has been accomplished in our laboratory by Anna Helgason.[178] Unlike Kakisawa's route, however, this approach employs a convergent aromatic annulation strategy for the construction of the tricyclic core of **335**. Previous work in our laboratories has demonstrated that annulation strategies based on the addition of vinylketenes to activated acetylenes are useful for the preparation of various mono- and polycyclic aromatic natural products;[179] Helgason's application of this approach is outlined below in Scheme 54.

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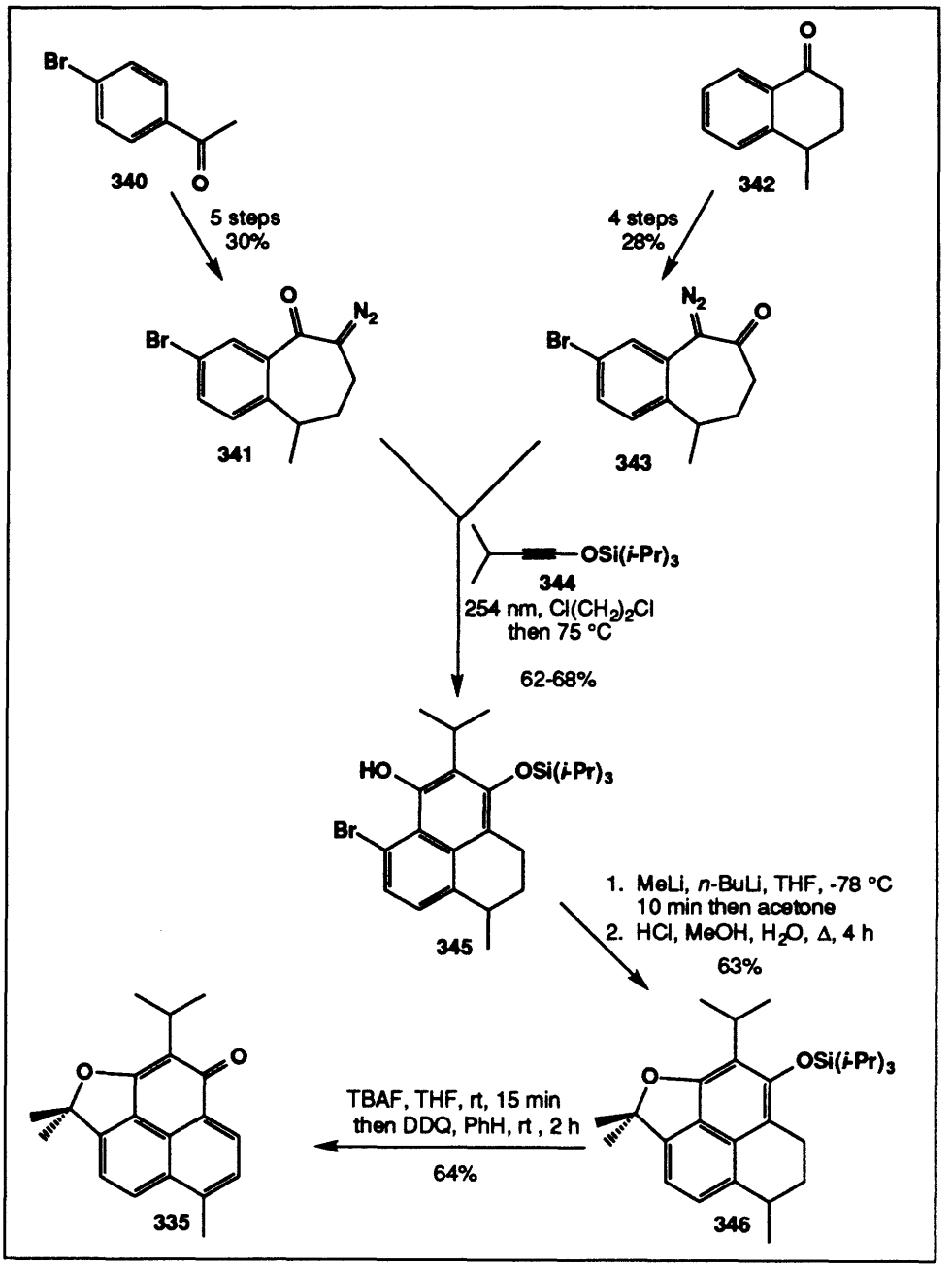
[178]Helgason, A. L. Ph. D. Thesis, Massacusetts Institute of Technology, May 1994.

[179](a) Danheiser, R. L.; Gee, S. K.; *J. Org. Chem.* **1984**, *49*, 1672. (b) Danheiser, R. L.; Gee, S. K.; Perez, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 806. (c) Danheiser, R. L.; Nishida, A.; Savariar, S.; Trova, M. P. *Tetrahedron Lett.* **1988**, *29*, 4917. (d) Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *J. Am. Chem. Soc.* **1990**, *112*, 3093. (e) Danheiser, R. L.; Cha, D. D. *Tetrahedron Lett.* **1990**, *31*, 1527. (f) Danheiser, R. L.; Casebier, D. S.; Loebach, J. L. *Tetrahedron Lett.* **1992**, *33*, 1149.

Scheme 54



An attractive feature of Helgason's strategy is that either diazo benzosuberone derivative **341** or **343** can function as the vinylketene precursor. Both of these compounds can be readily produced in multigram quantities from commercially available starting materials. Irradiation of either **341** or **343** in the presence of the silyloxyacetylene

derivative **344** followed by heating for several hours provided the key tricyclic core of salvilenone via a cascade of four pericyclic reactions. The final ring of **335** was created by a metal-halogen exchange reaction on **345** to provide an aryllithium species which was quenched with acetone; treatment of the resulting tertiary alcohol derivative with acid closed the furanyl ring. Desilylation of **346** with tetrabutylammonium fluoride, followed by oxidation with 2,3-dichloro-4,5-dicyanobenzoquinone provided salvilenone as a bright yellow solid. Although Helgason's route to **335** does not proceed in a significantly greater overall yield than Kakisawa's (9-11% versus 8.5%), it is much shorter (8-9 steps versus 14 steps).

Cycloaddition Approaches to Salvilenone

In early 1993, we became interested in the synthesis of salvilenone as the showcase for another method developed in our laboratories. As shown in Scheme 55, this new process involves the intramolecular [4+2] cycloaddition reaction of conjugated enynes to provide aromatic products via high energy intermediates.[180] In some respects, this transformation is similar to another class of reactions of highly unsaturated conjugated systems known as the "cycloaromatizations".[181] Unlike these processes, however, this new method appears to be a synthetically useful reaction for the construction of six-membered rings. An examination of the enyne literature reveals several previous reports of

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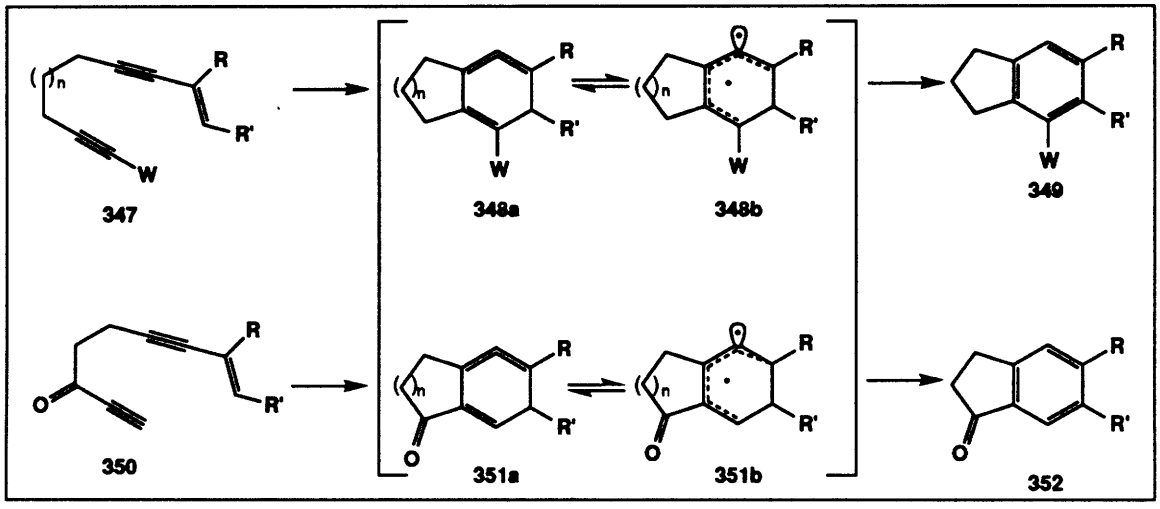
[180]Danheiser, R. L.; Gould, A. E.; Fernandez, R. I.; Helgason, A. L. *J. Am. Chem. Soc.*, submitted for publication.
[181]Nicolaou, K. C.; Dai, W. -M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1387 and references cited therein.

processes related to this new method, including the dimerization of arylpropiolic acids first noted by Michael and Bucher in 1895.[182,183]

Scheme 55



The feasibility of this process was first demonstrated in our laboratories by Alexandra Gould; she discovered that the thermolysis of the acetylenic ketone derivative **353** at 180 °C for 7 h provided the expected hydrindane **354** in good yield (Scheme 56). It was also noted that the inclusion of phenols had a beneficial result on the yield of the reaction. In the presence of excess zinc(II) bromide, this cycloaddition reaction occurred at much lower temperatures. The scope of this "Type I" reaction, as determined by Gould, is quite broad; a variety of electron-deficient alkynes will undergo this reaction readily, while less activated derivatives can be encouraged to react at higher temperatures.

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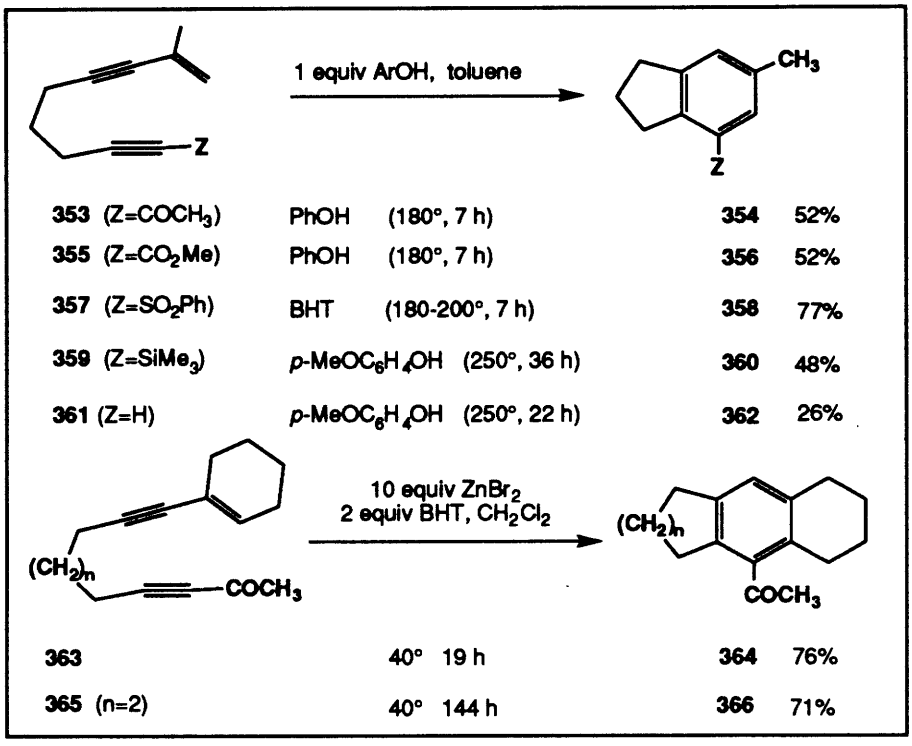
[182](a) Michael, A.; Bucher, J. E. *J. Chem. Soc.* **1895**, *28*, 2511. (b) Michael, A.; Bucher, J. E. *Amer. Chem. J.* **1898**, *20*, 89. For later developments, see: (c) Haworth, R. D.; Kelly, W. *J. Chem. Soc.* **1936**, 745. (d) Badder, F. G.; El-Assal, L. S.; Doss, N. A. *J. Chem. Soc.* **1959**, 1027. (e) Brown, D.; Stevenson, R. *J. Org. Chem.* **1965**, *30*, 1759. (f) Cadby, P. A.; Hearn, M. T. W.; Ward, A. D. *Aust. J. Chem.* **1973**, *26*, 557 and references cited therein.

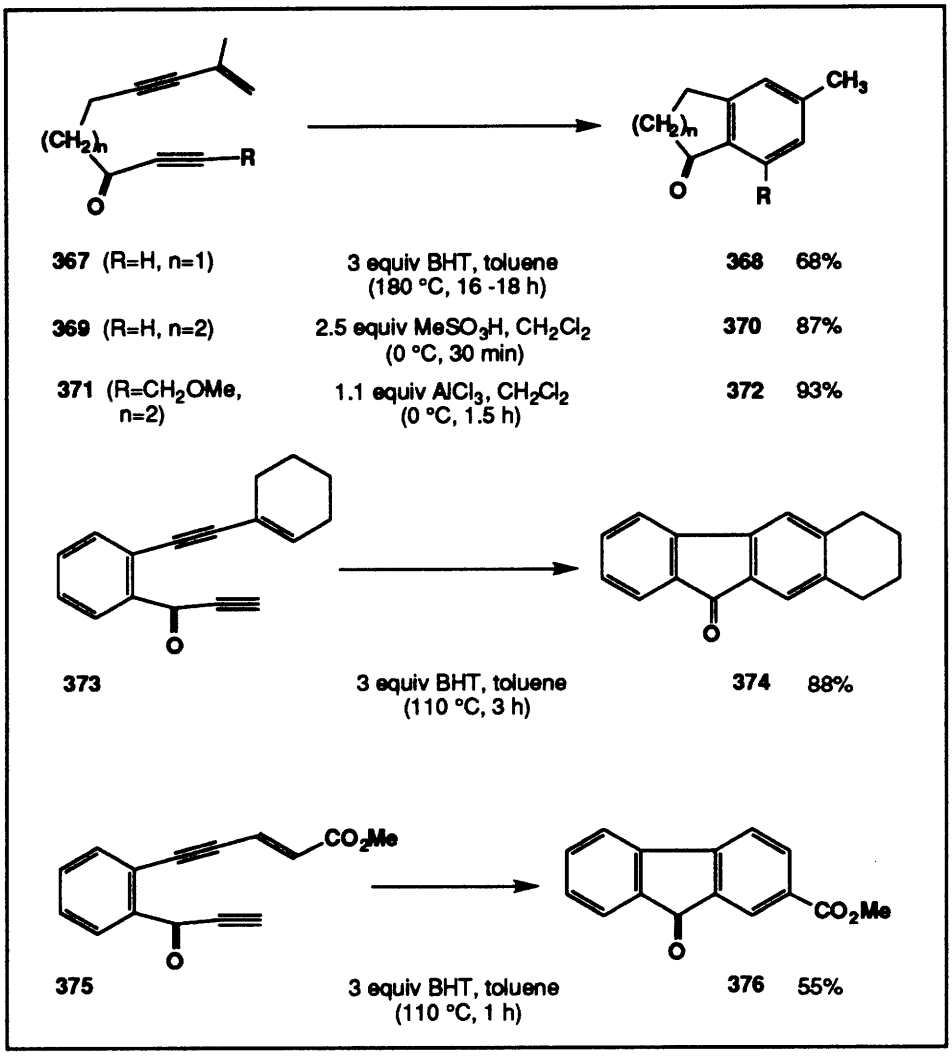
[183]All of these intramolecular reactions involve oxygen in the connecting chain: (a) Johnson, A. W. *J. Chem. Soc.* **1945**, 715. (b) Hakopian, L. A.; Gesalian, G. I.; Grigorian, S. G.; Matsoyan, S.G. *Arm. Khim. Zh.* **1974**, *27*, 764. (c) Hakopian, L. A.; Gezalian, G. I.; Matsoyan, S. G. *Arm. Khim. Zh.* **1974**, *27*, 768.

Scheme 56



Shortly after the initial discovery of this reaction, Roberto Fernandez and Anna Helgason began to explore the "Type II" cycloadditions. Some representative examples are shown below in Scheme 57. Here, the activating group is incorporated in the chain linking the enyne and the "enynophile". For this class of substrates, it has been observed that both protic and Lewis acids are capable of promoting the cycloaddition, enabling most of these reactions to be conducted under more mild conditions than for the "Type I" cases.

Scheme 57

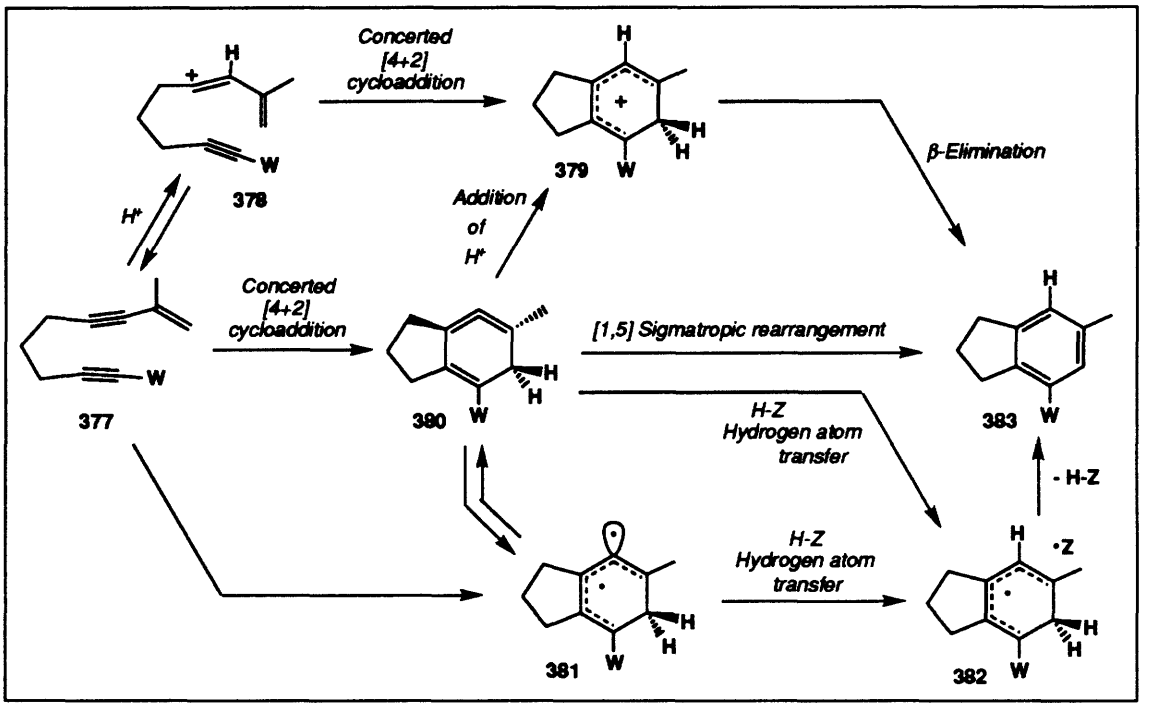


Presently, a number of pathways seem possible for these conversions (Scheme 58); studies are currently underway in our laboratories to determine the mechanism of this intriguing reaction. The concerted [4+2] cycloaddition to give the strained cyclic allene derivative **380** is one possibility.[184] At elevated temperatures, **380** may exist in equilibrium with its biradical counterpart **381**, or the initial cyclization may proceed directly

[184]The first reference to a cyclic allene intermediate in the context of an enyne cycloaddition should be credited to Butz, see Butz, L.; Geddis, A. M.; Butz, E. W. J.; Davis, R. E. *J. Org. Chem.* **1940**, *5*, 379.

to this biradical intermediate in a fashion akin to the previously mentioned "cycloaromatization" reactions.

Scheme 58



The ability of protic acids to promote this reaction suggests that initial formation of a butadienyl cationic species (such as **378**), followed by a concerted [4+2] cycloaddition to provide **379** is also a reasonable alternative.[185] The isomerization of the proposed intermediates to the observed product can occur via several different mechanisms. It should be noted that the possibility that multiple pathways are operative in these reactions (depending on the reaction conditions) cannot be excluded.

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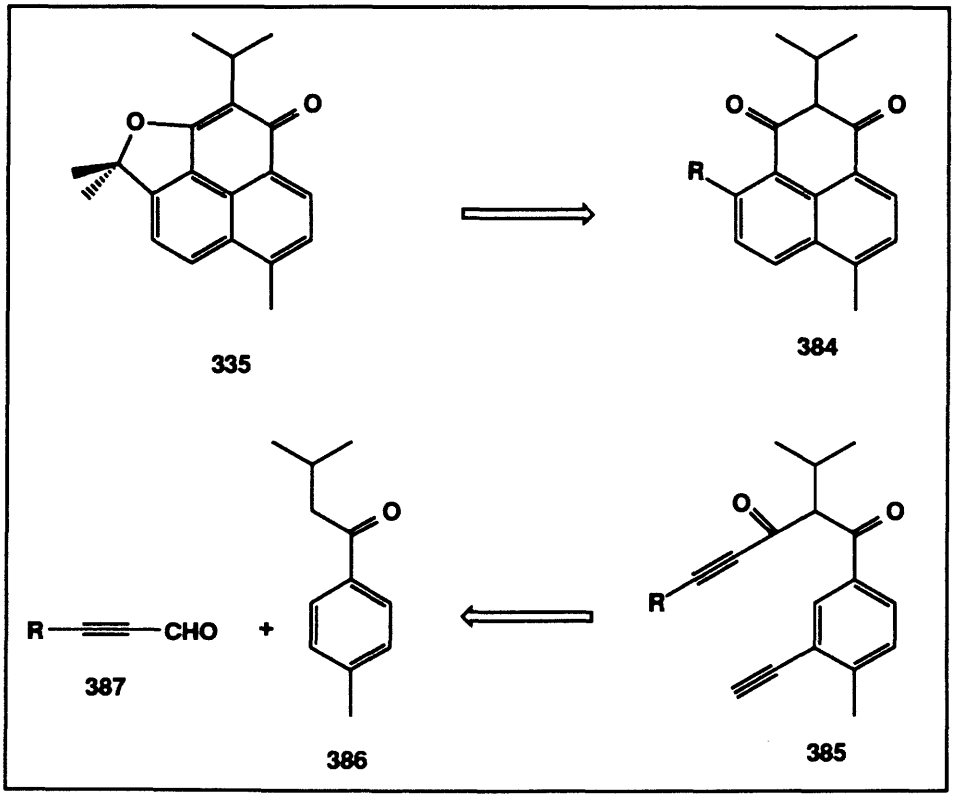
[185](a) For the inital discussion of the butadienyl cation pathway, see: Nazarov, I. N.; Verkholetova, G. P.; Torgov, I. V. *J. Gen. Chem. USSR (Engl. Transl.)* **1959**, *29*, 3277. For other discussions of this mechanism, see: (b) Whitlock, H. W., Jr.; Wu, E. M.; Whitlock, B. J. *J. Org. Chem.* **1969**, *34*, 1857. (c) Hoffmann, H. M. R.; Krumwiede, D.; Mucha, B.; Oehlerking, H. H.; Prahst, G. W. *Tetrahedron* **1993**, *49*, 8999.

An Approach to Salvilenone Based on the [4+2] Enyne Cycloaddition

The retrosynthetic analysis for our approach to salvilenone using the [4+2] enyne cycloaddition strategy is shown below in Scheme 59. The tricyclic intemediate **384** was viewed as the key target for this synthesis, as closure of the furanyl ring via a number of different methods (depending on the nature of R) should be straightforward. Intermediate **384** was envisioned as arising from the intramolecular [4+2] cycloaddition reaction of the conjugated aryl acetylene derivative **385**. This diketone intermediate was thought to be easily obtainable from 4-methylisovalerylphenone (**386**) and a variety of acetylenic aldehydes **387** via aldol condensation followed by oxidation. The following chapter contains the details of the synthesis of various cycloaddition substrates. Preliminary results on the key [4+2] cycloaddition reaction are also presented.

Scheme 59



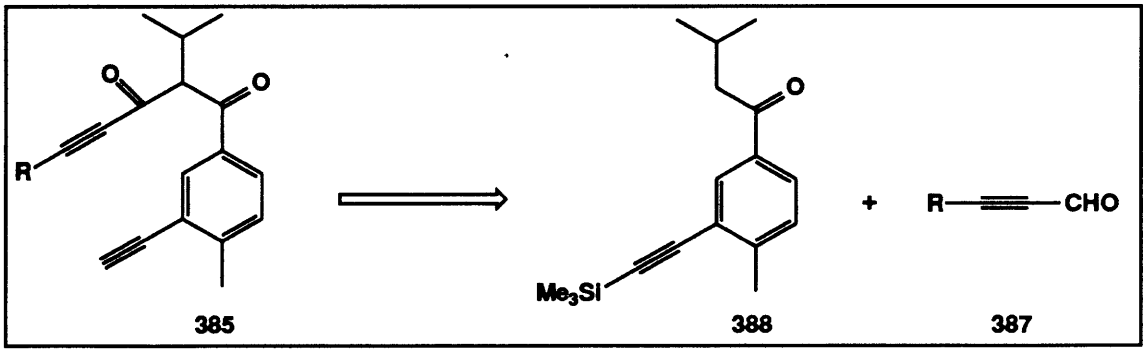
CHAPTER 2

Synthetic Approaches to Salvilenone

Preparation of Cycloaddition Substrates

As described in the preceding chapter, our new approach to salvilenone required the synthesis of various cycloaddition substrates of the general type represented by **385**. It appeared that the most straightforward method available to accomplish this task would involve aldol-type reactions between the aryl ketone derivative **388** and suitable substituted acetylenic aldehydes (Scheme 60). This strategy would permit us to easily modify the nature of the R group, allowing us to more fully explore the key cycloaddition step. Thus, developing efficient syntheses of these materials became our first priority.

Scheme 60



The aryl ketone derivative **388** was assembled in three steps as outlined below in Scheme 61. The Friedel-Crafts acylation of toluene with isovaleryl chloride, which had previously been described by Nightingale and Shanholtzer, provided the *p*-substituted

derivative **389** in 83% yield.[186] Electrophilic iodination of deactivated arenes[187] with iodine tris(trifluoroacetate) has been reported to proceed in good to excellent yield.[188] Reaction of this reagent (prepared by the oxidation of iodine in trifluoroacetic anhydride with fuming nitric acid[189]) with **387** in dichloromethane at room temperature for 18 h, followed by reduction of the intermediate bis(trifluoroacetoxy)iodoarene species with aqueous sodium iodide furnished the expected 3-iodo derivative **390** in good yield after flash chromatography. The regiochemistry of this reaction was confirmed by examination of the coupling constants of the aromatic protons in the ^1H NMR spectrum. Furthermore, a comparison of the chemical shifts of the aromatic carbons in the ^{13}C NMR spectrum with calculated values supported the assigned structure. Other iodinating procedures, such as the bis(pyridine)iodonium(I) tetrafluoroborate-CF_3CO_2H system[190] or the iodine-$PhI(O_2CCF_3)_2$ protocol[191], have been used with deactivated aromatics. Because the former procedure employs strongly acidic conditions, its use in iodinating substrates bearing enolizable ketones is limited. Application of the latter procedure to our substrate resulted in no reaction. The final step in this sequence involved the installation of the acetylene moiety via the Hagihara modification of the Castro-Stephens reaction.[192] Treatment of **390** with (trimethylsilyl)acetylene in the presence of a catalytic amount of bis(triphenylphosphine)palladium(II) chloride and copper(I) iodide in diethylamine at room temperature led to a rapid consumption of the starting material. Standard aqueous workup and flash chromatography of the crude product provided the desired acetylene derivative **388** in excellent yield. An even faster reaction was noticed when Farina's catalyst system

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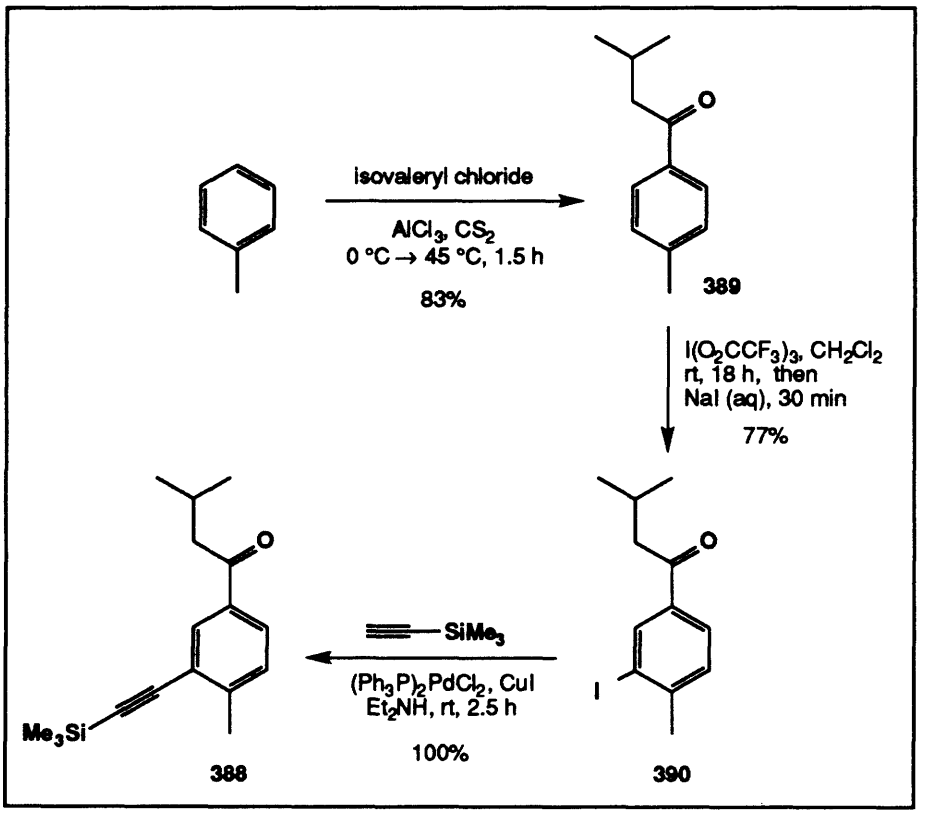
[186]Nightingale, D.; Shanholtzer, O. G. *J. Org. Chem.* **1942**, *7*, 6.
[187]For a recent review of the synthesis of iodoaromatics, see Merkushev, E. B. *Synthesis* **1988**, 923.
[188]Fukuyama, N.; Nishino, H.; Kurosawa, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4363.
[189]Schmeisser, M.; Dahmen, K.; Sartori, P. *Chem. Ber.* **1967**, *100*, 1633.
[190]Barluenga, J.; Gonzalez, J. M.; Garcia-Martin, M. A.; Campos, P. J.; Asensio, G. *J. Org. Chem.* **1993**, *58*, 2058.
[191]Merkushev, E. B.; Simakhina, N. D.; Koveshnikova, G. M. *Synthesis* **1980**, 486.
[192](a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627.

($Pd_2(dba)_3$-tris(2-furyl)phosphine, *vide supra*) was employed; under these conditions the coupling reaction of **390** with TMS acetylene was complete in 10 min.

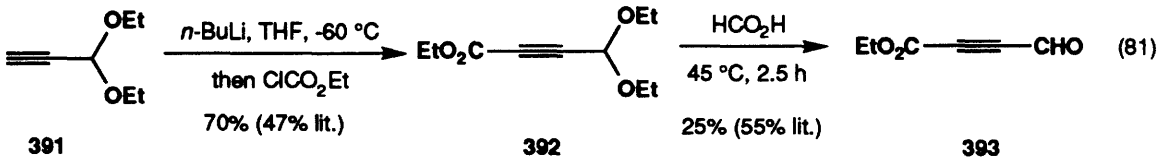
Scheme 61



With the desired aryl ketone in hand, our attention turned toward the synthesis of various acetylenic aldehydes. We were initially interested in derivatives in which R was an electron-withdrawing group, as we believed that this would provide additional activation of the acetylene in the [4+2] cycloaddition reaction. Gorgues and coworkers had previously described a two-step synthesis of a suitable acetylene derivative **393** (eq 81).[193] We found that by conducting the carboalkoxylation reaction under more dilute conditions than those employed by Gorgues, significant increases in the yield of this step were achieved (70% versus 47%). Thus, treatment of **391** with *n*-BuLi in tetrahydrofuran at -60 °C followed by the addition of ethyl chloroformate provided **392** as a clear liquid after distillation.

[193]Gorgues, A.; Simon, A.; Le Coq, A.; Hercouet, A.; Corre, F. *Tetrahedron* **1986**, *42*, 351.

Heating **392** in formic acid at 45 °C for 2.5 h effected hydrolysis to the desired aldehyde. Neutralization of the reaction mixture with sodium bicarbonate followed by extractive workup and vacuum distillation provided the aldehyde **393** as a clear oil in 25% yield, significantly lower than the reported 55% yield. Attempts to modify this reaction by employing aqueous sulfuric acid-dimethylsulfoxide or Dowex 50-aqueous acetone were unsuccessful. The acetylene derivative **393** appears to undergo polymerization upon distillation, even at reduced pressure in the presence of BHT. Furthermore, purification by flash chromatography is not feasible, as **393** decomposes completely on silica gel or alumina. Once purified, this material can be stored as a dilute solution in hexane at 0 °C for approximately one week before extensive decomposition is noted.

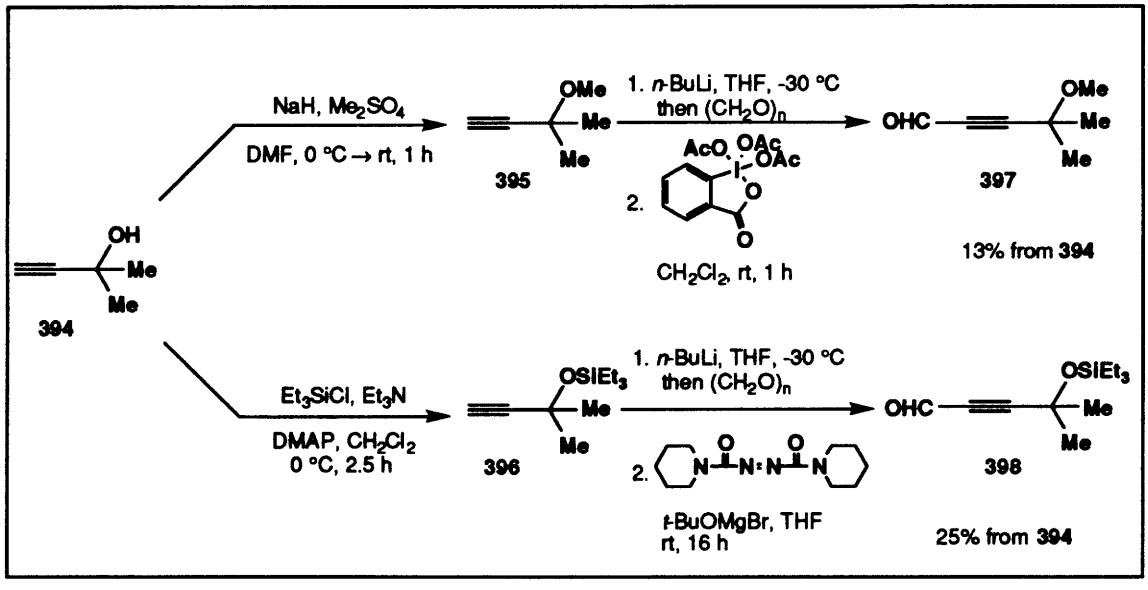


We were also interested in acetylenic aldehydes bearing protected alcohol functionalities. In particular, derivatives such as **397** and **398** were considered attractive since they offered a more convergent approach to salvilenone (Scheme 62). As shown below, the synthesis of both of these compounds was straightforward. Etherification of 2-methyl-3-butyn-2-ol (**394**) with either dimethyl sulfate[194] or chlorotriethylsilane[195] provided the known acetylenes in good yield. Metallation of either **395** or **396** with *n*-BuLi in tetrahydrofuran at -30 °C followed by quenching of the intermediate lithium acetylide with paraformaldehyde furnished the corresponding primary alcohol derivatives as clear oils after flash chromatography. Oxidation of **395** with the Dess-Martin

[194]The synthesis of **395** using this procedure was previously reported by Corey, E. J.; Floyd, D.; Lipshutz, B. H. *J. Org. Chem.* **1978**, *43*, 3418.
[195]The synthesis of **395** was previously reported by Petrov, A. D.; Shchukovskaya, L. L.; Sadykh-Zade, S. I.; Egorov, Y. P.; *Doklady Akad. Nauk. S.S.S.R.* **1957**, *115*, 522.

periodinane[196,197] in dichloromethane at room temperture for 1 h afforded the desired acetylenic aldehyde. The propargylic alcohol **396** was transformed to the corresponding aldehyde **394** using the method of Saigo.[198] Thus, formation of the magnesium salt of **396** by treatment with *t*-butyoxymagnesium bromide in tetrahydrofuran at room temperature followed by the addition of the 1,1'-(azodicarbonyl)dipiperidine resulted in the formation of **394**. As expected, these compounds proved to be much more stable than **393** and could be purified by flash chromatography.

Scheme 62



One final aldehyde substrate was synthesized for our studies (eq 82). Silylation of (±)-3-butyn-2-ol (**399**) with *t*-butyldimethylsilyl chloride provided the known ether in excellent yield.[199] This compound was converted to the corresponding aldehyde in good yield by employing the procedure of Iguchi.[200] Metallation of **400** with *n*-BuLi in tetrahydrofuran at -78 °C followed by the addition of boron trifluoride etherate and *N,N*-

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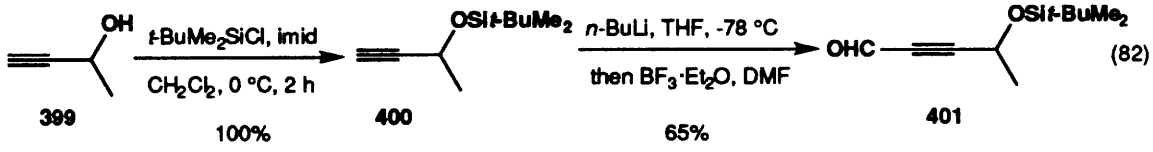
[196]Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
[197]The author is deeply indebted to Professor Scott C. Virgil for supplying large quantities of the Dess-Martin reagent.
[198]Narasaka, K.; Morikawa, A.; Saigo, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2773.
[199]The synthesis of **400** was previously reported by Hashimoto, S.; Miyazaki, Y.; Shinoda, T.; Ikegama, S.; *J. Chem. Soc., Chem. Commun.* **1990**, 1100.
[200]Iguchi, K.; Kitade, M.; Kashiwagi, T.; Yamada, Y. *J. Org. Chem.* **1993**, *58*, 5690.

dimethylformamide furnished **401** after standard aqueous workup and flash chromatography. This derivative proved to be as stable as both **397** and **398.**

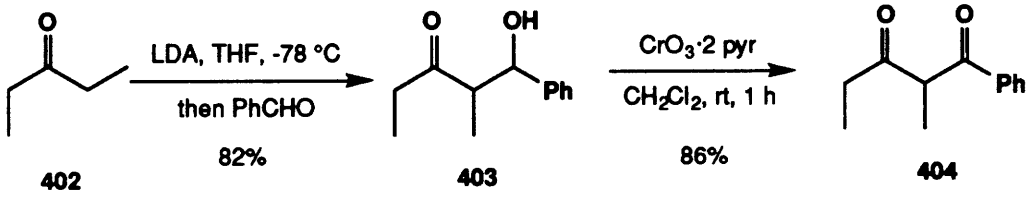


First Generation Approaches to Salvilenone

With the necessary components in hand, we began to examine the synthesis of the key cycloaddition substrates via the aldol condensation-oxidation strategy. This approach, to the synthesis of 1,3-dicarbonyl compounds, shown below in eq 83, has previously been employed by Smith[201] and Yamauchi.[202] For example, 3-pentanone (**402**) was converted to the 1,3-diketone derivative **404** by condensation of its lithium enolate with benzaldehyde followed by oxidation of the β-hydroxyketone **403** with the Collins reagent. As outlined in Scheme 63, we initially decided to examine the substrate in which the acetylene was substituted with the electron-withdrawing carboethoxy group; thus, the aldehyde derivative **393** was chosen as the electrophile for the aldol reaction. A simple model study employing propiophenone and **393** demonstrated that this aldol reaction was indeed feasible.[203] Formation of the lithium enolate of propiophenone with LDA followed by the addition of **393** as a solution in tetrahydrofuran furnished **408** in moderate yield after flash chromatography. The β-hydroxy ketone was then subjected to a number a oxidizing conditions. Treatment of **408** with pyridinium chlorochromate-sodium acetate, chromium trioxide-sulfuric acid-aqueous acetone (Jones' reagent),[204] chromium trioxide-pyridine,[201] *N*-iodosuccinimide-tetrabutylammonium iodide,[205] the Dess-Martin reagent,[196] barium

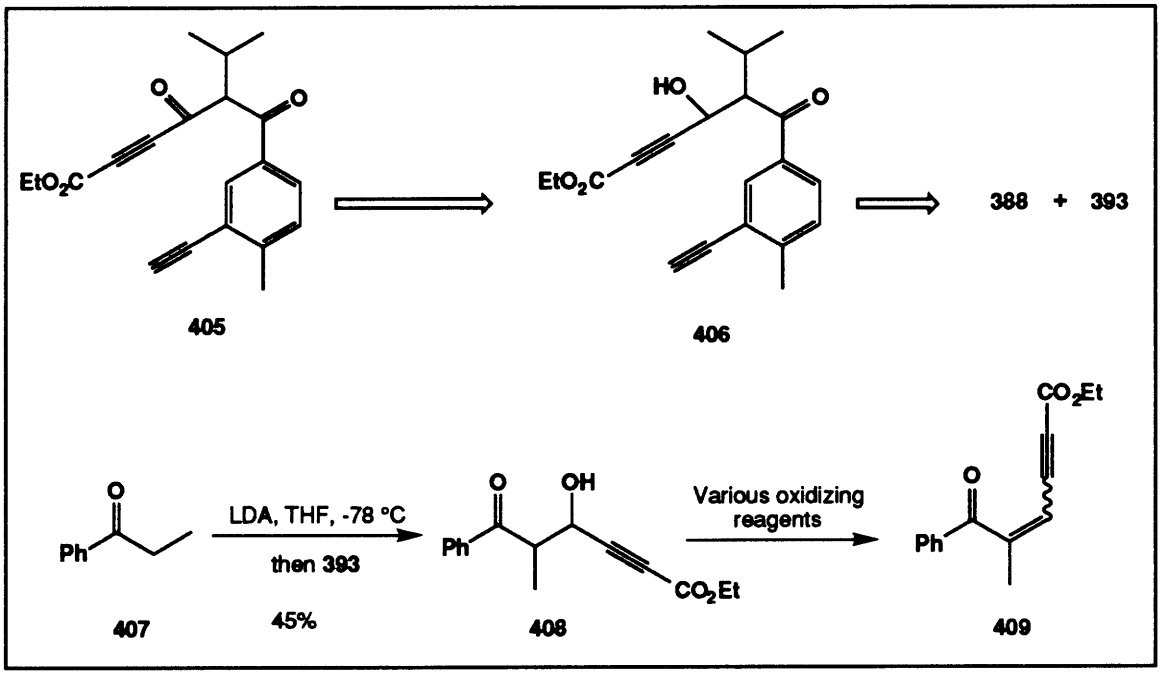
[201]Smith, A. B., III.; Levenberg, P. A. *Synthesis* **1981**, 567.
[202]Katayama, S.; Fukuda, K.; Watanabe, T.; Yamauchi, M. *Synthesis* **1988**, 178.
[203]For some recent examples of aldol reactions with acetylenic aldehydes, see: (a) Suffert, J. *Tetrahedron Lett.* **1990**, *31*, 7437. (b) Petasis, N. A.; Teets, K. A. *Tetrahedron Lett.* **1993**, *34*, 805.
[204]Zibuck, R.; Streiber, J. *Org. Synth.* **1992**, *71*, 236.
[205]Hanessian, S.; Wong, D. H.; Therien, M. *Synthesis* **1981**, 394.

manganate,[206] or tetrapropylammonium perruthenate[207] led to conversion of the starting material to a bright yellow oil. Analysis of both the IR and ^{1}H NMR of this compound indicated that this was the elimination product **409**, not the desired 1,3-diketone.



(83)

Scheme 63



While these results suggested that the synthesis of **405** via this route was not feasible, we wondered if the β-hydroxy ketone derivative **406** would be a suitable "Type I" cycloaddition substrate (Scheme 64). Using the aldol conditions describe above for the model compound, **410** was produced in poor yield. Modification of the reaction by

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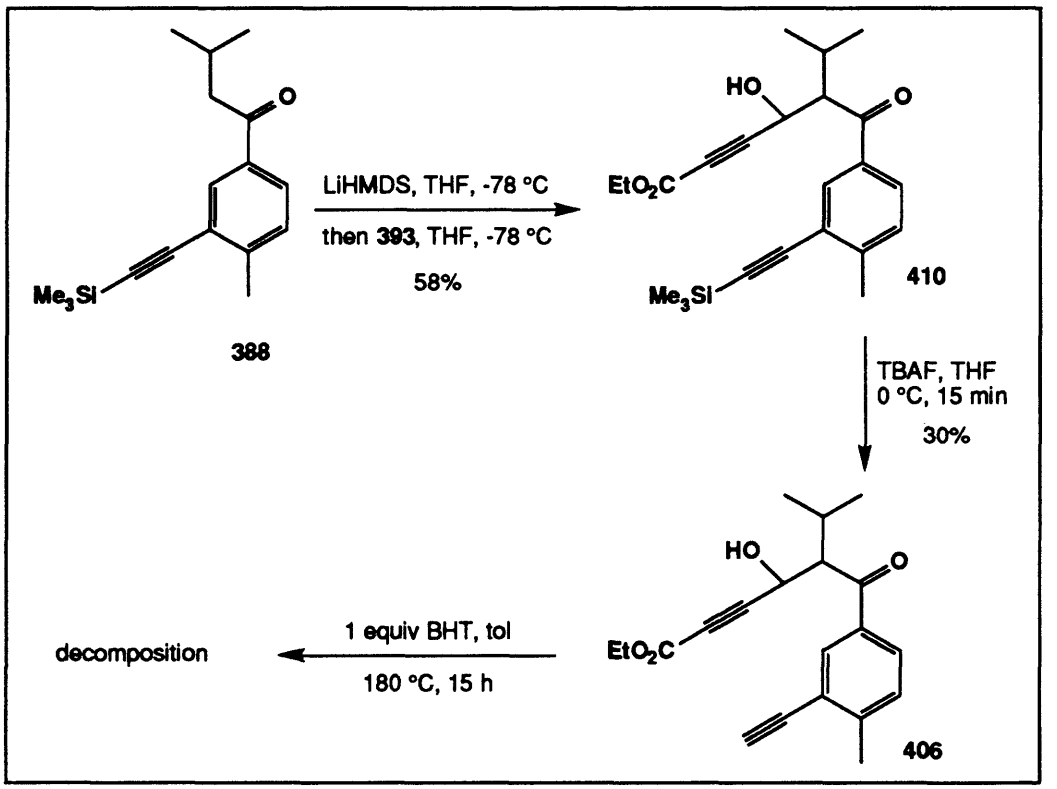
[206]Firouzabadi, H.; Ghaderi, E. *Tetrahedron Lett.* **1978**, 839.
[207]Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625.

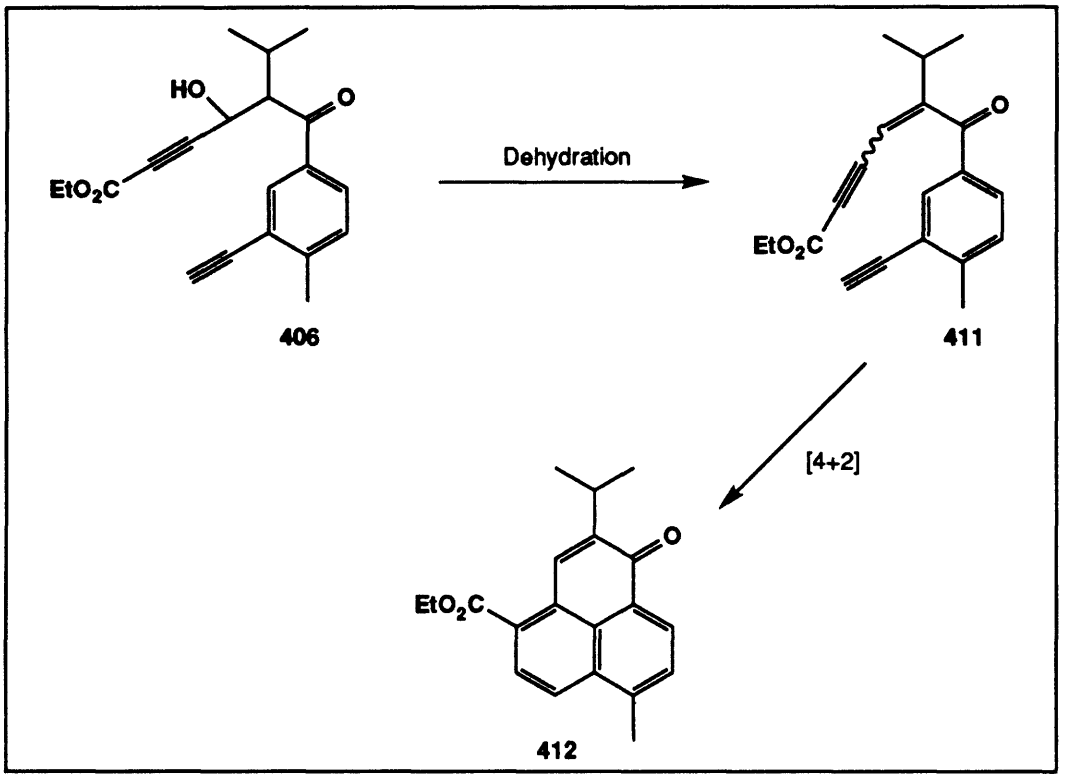
employing LiHMDS as the base and precooling the aldehyde solution to -78 °C prior to its addition to the enolate provided dramatic improvements in yield (58% versus 25%). Deprotection of the acetylene by treatment of **410** with tetrabutylammonium fluoride in tetrahydrofuran gave **406** in low yield; under these basic conditions, most of the starting material decomposed via a retroaldol reaction. Unfortunately, thermolysis of **406** under the standard conditions for "Type I" cycloadditions (180 °C in degassed toluene, 1 equiv of BHT, 15 h, *vide supra*) led to complete decomposition of the starting material.

Scheme 64



Based on the easy dehydration of β-hydroxyketone **405**, we wondered if a similar transformation of **406** to **411** would provide a suitable cycloaddition substrate (Scheme 65). Some preliminary experiments concerning the synthesis of **411** have been conducted, but at this time no meaningful conclusions can be drawn from them.

Scheme 65

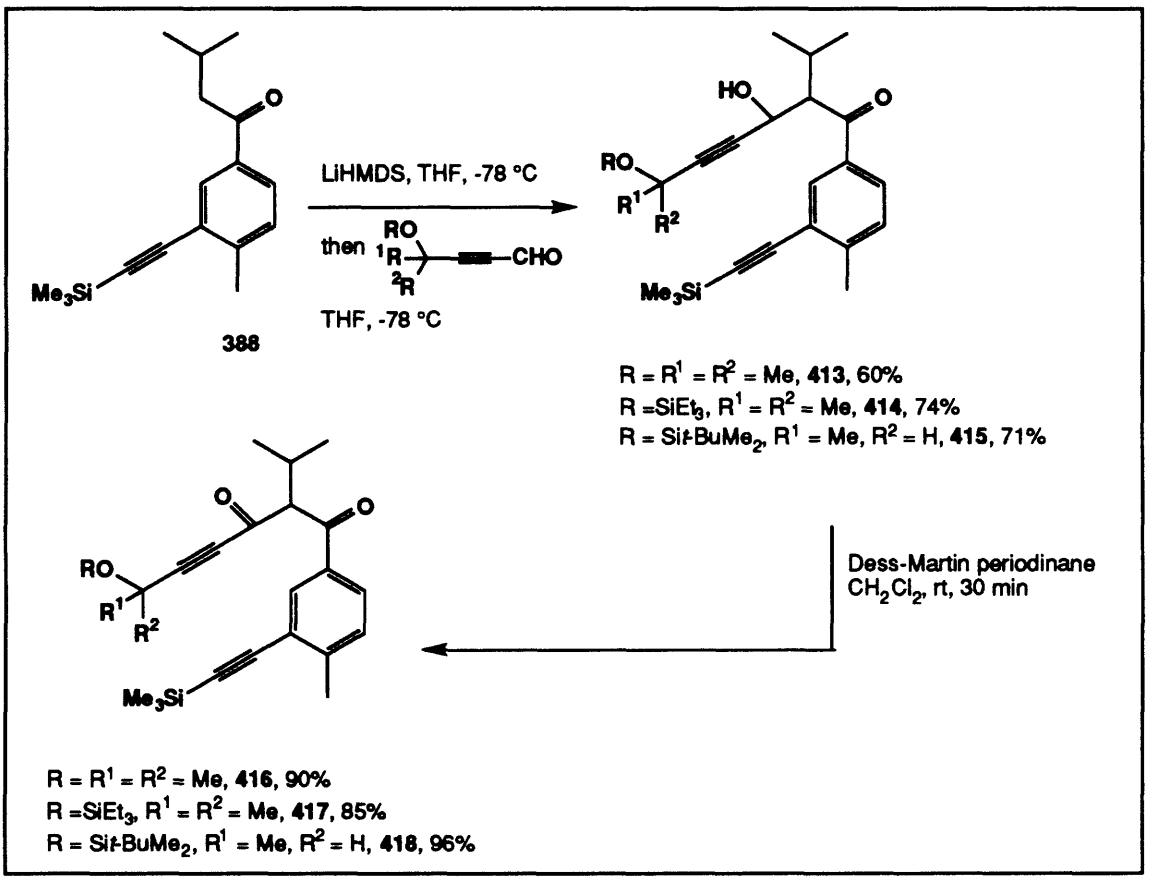


Second Generation Approaches to Salvilenone

We believe that our inability to oxidize **408** to the corresponding 1,3-diketone was due in large part to the presence of the ester functionality. It was thought that by employing the aldehydes which lack this extra activating group, we could circumvent this problem. Thus, as shown in Scheme 66, we began to examine the synthesis of other cycloaddition substrates. Aldol condensation of **388** with the aldehydes **397**, **398** and **401** under the conditions described above (LiHMDS, aldehyde precooled to -78 °C prior to addition) provided good yields of the desired β-hydroxy ketones. In all of these cases, oxidation with the Dess-Martin reagent at room temperature in dichloromethane led to a rapid

consumption of the starting material. Flash chromatography of the crude reaction products provided the desired 1,3-diketones in excellent yield.

Scheme 66

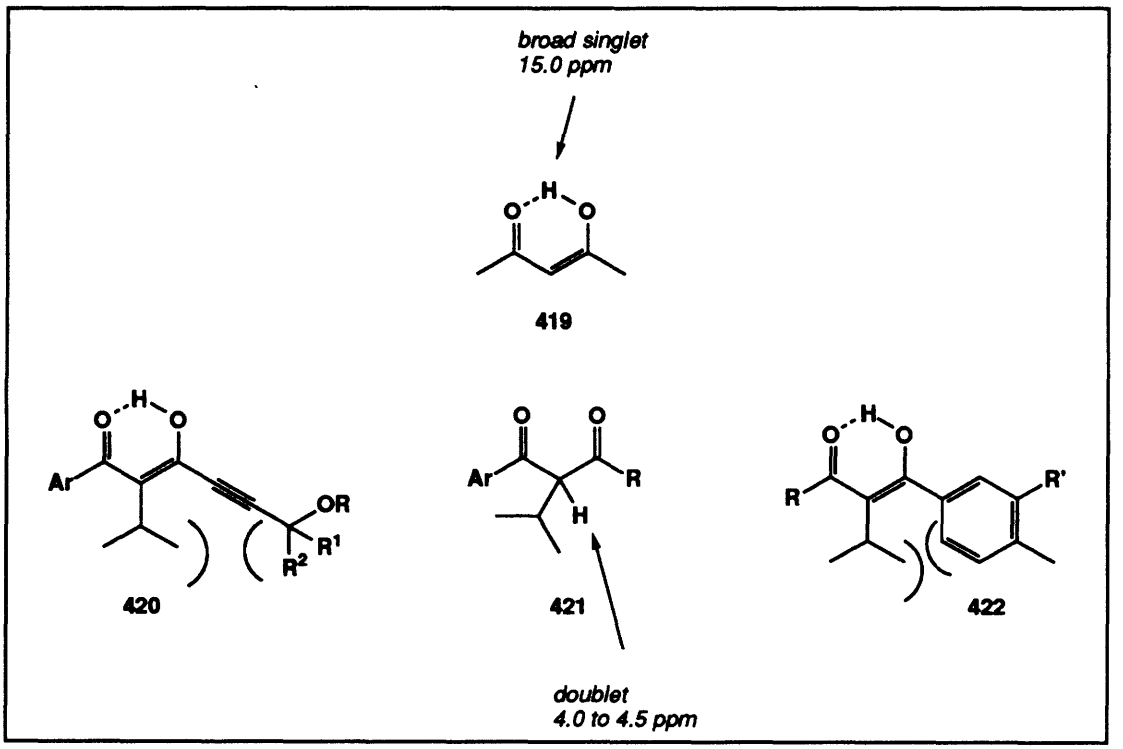


Both IR and ^{13}C NMR spectra of the oxidation products confirmed the presence of 2 distinct carbonyl groups, lending credence to the proposed structures. However, as shown in Scheme 67, these three compounds did not exhibit a feature normally observed in ^{1}H NMR spectra of acyclic 1,3-diketones. For instance, the ^{1}H NMR spectrum of acetylacetone (**419**) in $CDCl_3$ shows a peak at 15.0 ppm, indicating that **414** exists in enolic form.[208] While the spectra of **416-418** in $CDCl_3$ do not contain this peak, they do possess a clean doublet between 4.0-4.5 ppm, suggesting that these compounds do not

[208]Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds, 4th Edition;* John Wiley and Sons: New York, 1981; pp 196-197.

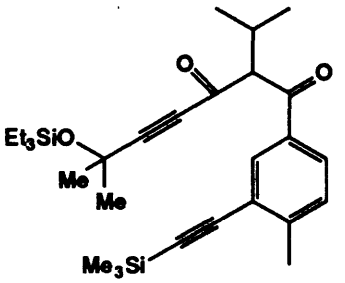
exist in the enol form. For these derivatives, it seems likely that adopting an enol tautomer would require an unfavorable steric interaction between the bulky isopropyl group and either the aryl ring or the acetylene moiety. Thus, these compounds exist in the keto form, and the proton between the two carbonyl groups appears as a doublet.

Scheme 67

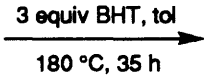


From these three 1,3-diketones, several options for the [4+2] cycloaddition reaction seemed possible. Direct thermolysis of **418** (eq 84) under the standard "Type I" conditions (180 °C in toluene, 3 equiv BHT, 35 h) led only to the recovery of unchanged starting material. On the other hand, treatment of this compound with dimethylaluminum chloride in dichloromethane at -78 °C gave a complex mixture of products (TLC analysis indicated that more than 10 new compounds were formed). We believed that some of the difficulties encountered in these two reactions were due to the presence of the bulky trimethylsilyl group on the enyne and the large tertiary alcohol group on the "enynophile". Since these substituents must be *ortho* to each other on the newly formed six-membered

ring, it seemed likely that an unfavorable steric interaction could be preventing the cycloaddition.



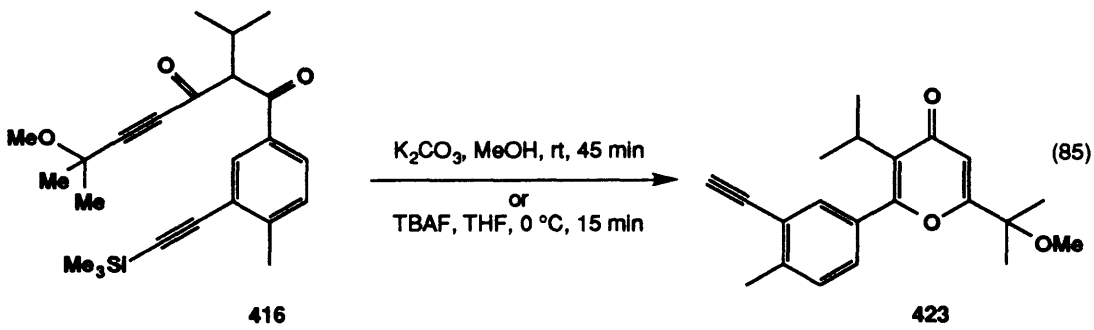
418



no reaction (84)

In order to reduce this possible steric problem, we decided to deprotect the (trimethylsilyl)acetylene of **416**. As shown below in eq 85, treatment of this compound with a catalytic amount of potassium carbonate in methanol or with 1 equiv of tetrabutylammonium fluoride in tetrahydrofuran resulted in the formation of a product which had indeed been desilylated. A careful spectroscopic examination of the this compound, however, indicated that this material was not the expected 1,3-diketone. The IR spectrum indicated that only one acetylene was present; strong absorptions at 1680 cm^{-1} (doublet) and 1620 cm^{-1} were also noted. The ^{13}C NMR spectra showed that onyl carbonyl group (187 ppm) was present, while ^{1}H NMR revealed one new olefinic proton (6.05 ppm). Based on this data, we concluded that this new compound was the γ-pyrone derivative **423**.[209]

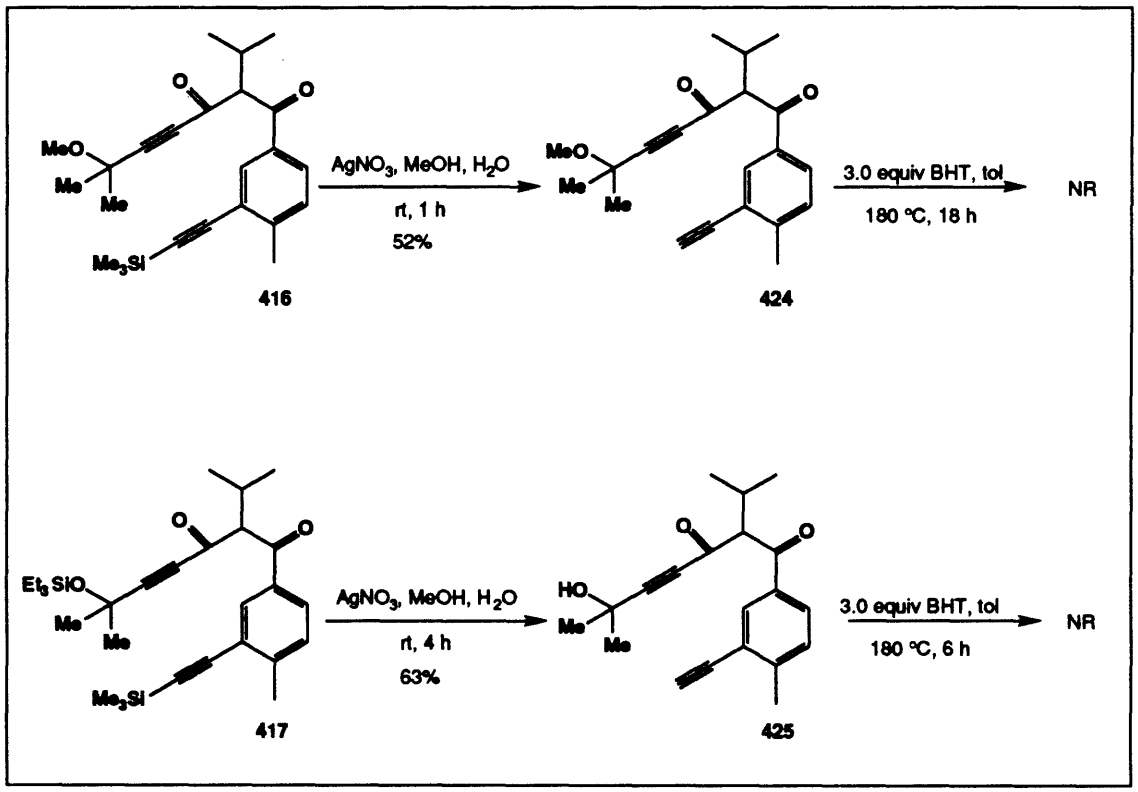
[209]Some related γ-pyrone derivatives prepared by treatment of acetylenic β-keto amides with acid were recently reported by Morris and coworkers. These compounds had the following spectral characteristics: carbonyl IR stretch 1650 cm^{-1}; ^{13}C NMR for carbonyl carbon 180 ppm. See Morris, J.; Wishka, D. G. *Synthesis* **1994**, 43.



416 423

Deprotection of the TMS acetylene moiety of **416** with a catalytic amount of silver(I) nitrate,[210] as shown in Scheme 68, provided the desired desilylated compound **424** in moderate yield. In an analogous fashion, the reaction of **417** with silver(I) nitrate cleaved both silyl protecting groups to afford **425**.

Scheme 68



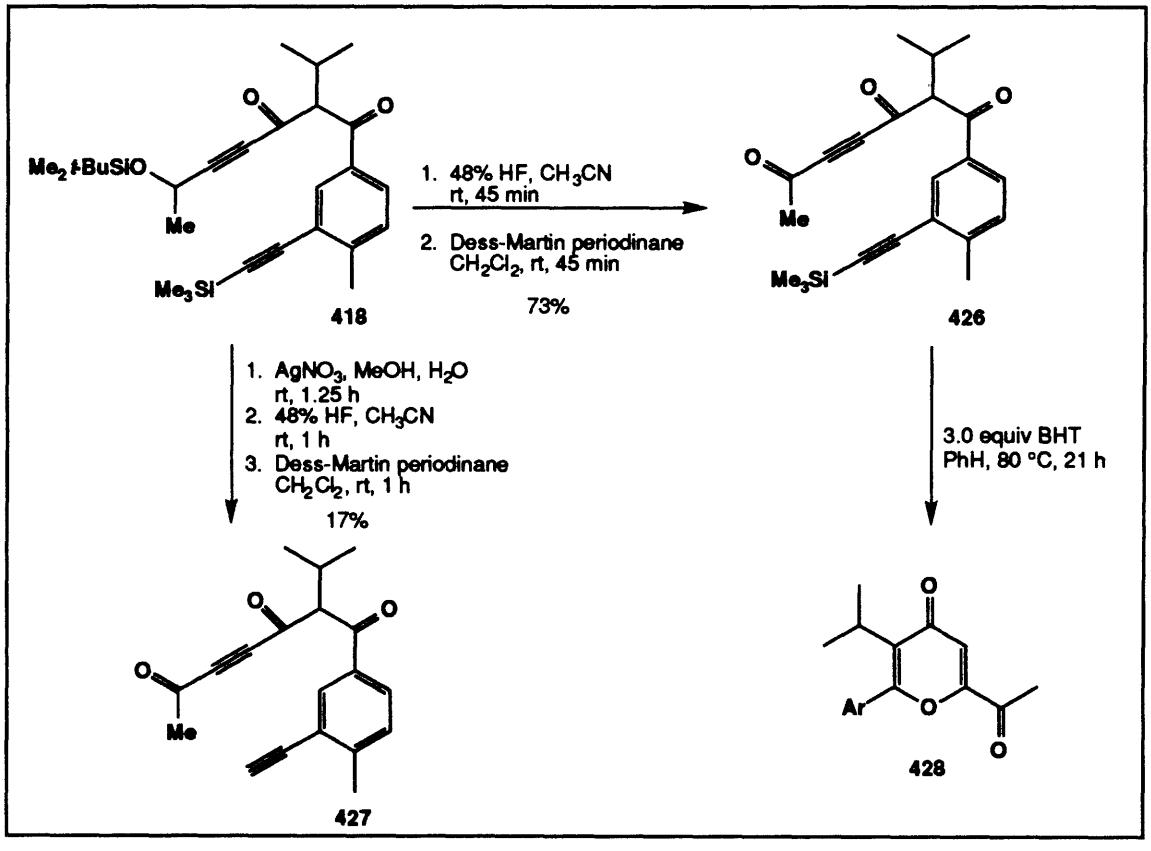
416 424 417 425

[210]Danheiser, R. L.; Tsai, Y. -M.; Fink, D. M. *Org. Synth.* **1988**, *66*, 1.

Unfortunately, thermolysis of either of these two compounds at 180 °C in toluene led solely to the recovery of unchanged starting material. Furthermore, treatment with protic acids seemed unlikely to provide the desired cycloaddition product, in light of Morris' report.

Recently, we have begun to reexamine the [4+2] cycloaddition reaction of substrates which contain doubly activated "enynophiles". As illustrated below in Scheme 69, the synthesis of the 1,3,6-triketones from **418** was relatively straightforward.

Scheme 69



Exposure of this compound to 48% aqueous hydrofluoric acid in acetonitrile at room temperature for 45 min resulted in the desilylation of **418** to give the corresponding alcohol derivative. Oxidation of this crude material with the Dess-Martin reagent in dichloromethane at room temperature provided **426** as a clear oil, in good overall yield from **418**. A similar 1,3,6-triketone (**427**) without the trimethylsilyl group was prepared by reaction of **418** with aqueous silver(I) nitrate, aqueous 48% hydrofluoric acid (to

remove TBDMS group), and oxidation with the Dess-Martin reagent. Both **426** and **427** were purified by flash chromatography; however, small amounts of the corresponding γ-pyrone derivatives were noted in the ^{1}H NMR spectra of these purified compounds. While this observation was rather foreboding, **426** was subjected to thermolysis (80 °C, benzene, 3 equiv of BHT). After 21 h, the 1,3,6-triketone **426** had been almost completely converted to γ-pyrone **428**.

In summary, we have begun exploring a new synthesis of salvilenone which relies upon a [4+2] cycloaddition of enynes as the key step. Presently, the research efforts are focused on the development of proper cycloaddition substrates and conditions which will allow the construction of the key tricyclic core of **335**.

Part III

Experimental Section

General Procedures

All reactions were performed in flame-dried glassware under a positive pressure of argon or nitrogen. Reaction mixtures were stirred magnetically unless otherwise indicated. Air and/or moisture sensitive reagents and solutions were transferred via syringe or cannula and were introduced into reaction vessels through rubber septa. Reaction product solutions were concentrated with the use of a Büchi rotary evaporator at approximately 20 mm Hg unless otherwise indicated.

Materials

Commercial grade reagents and solvents were used without further purification except as indicated below.

- Distilled under nitrogen, argon or vacuum from calcium hydride: acetonitrile, boron trifluoride etherate, dichloromethane, diethylamine, diglyme, diisopropylamine, dimethylsulfoxide, 1,1,1,3,3,3-hexamethyldisilazane, and *N*-methylpyrrolidinone.

- Distilled under nitrogen, argon, or vacuum from sodium benzophenone ketyl or dianion: benzene, diethyl ether, tetrahydrofuran, and toluene.

- Distilled under argon or nitrogen from quinoline: acetic anhydride.

Purification of other reagents was accomplished in the following manner; lithium chloride was dried at 130 °C (0.1 mmHg) for ca. 24 h; zinc chloride was refluxed in thionyl chloride for ca. 2 h, washed repeatedly with benzene, dried (0.1 mm Hg) for ca. 24 h and stored in a glove box.

Alkyllithium reagents were titrated in tetrahydrofuran or benzene at 0 °C with *sec*-butanol using 1,10-phenanthroline as an indicator.[211]

Diazomethane was generated from Diazald© using a Mini Diazald apparatus according to the procedure of Black.[212]

Rhodium(II) pivalate made prepared from rhodium(III) chloride by the procedure of Wilkinson.[213]

Chromatography

Analytical thin-layer chromatography (TLC) was performed on Merck pre-coated glass-backed silica gel 60 F - 254 0.25 mm plates. Visualization of spots was effected by one or more of the following techniques: (a) ultraviolet illumination, (b) exposure to iodine vapor, (c) immersion of the plate in a 10% solution of phosphomolybdic acid in ethanol followed by heating to ca. 200 °C, (d) immersion of the plate in an ethanolic solution of 3% *p*-anisaldehyde containing 0.5% concentrated sulfuric acid followed by heating to ca. 200 °C, and (e) immersion of the plate in an ethanolic solution of 3% *p*-vanillin containing 0.5% concentrated sulfuric acid followed by heating to ca. 200 °C.

Column chromatography was performed with the use of 230-400 mesh Merck or Baker silica gel·

Instrumentation

Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Boiling points are uncorrected.

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[211]Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.
[212]Black, T. H. *Aldrichim. Acta* **1983**, *16*, 3.
[213]Legzdins, P.; Mitchell, R. W.; Rempel, G. L.; Ruddick, J. D.; Wilkinson, G. *J. Chem. Soc.* **1970**, 3322.

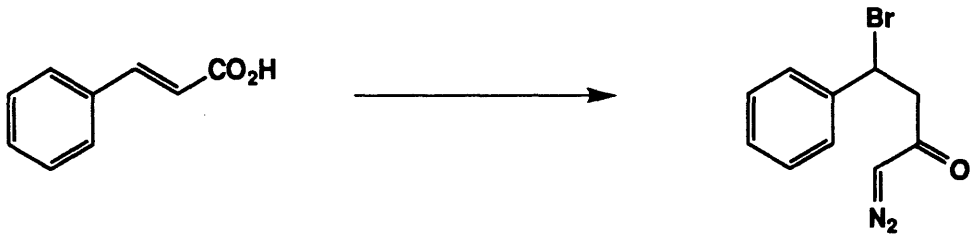
Infrared spectra (IR) were recorded using a Perkin-Elmer 1320 grating spectrophotometer.

^{1}H NMR spectra were recorded with Bruker AC-250 (250 MHz), Varian XL-300 (300 MHz) Varian Unity 300 (300 MHz), and Varian XL-500 (500 MHz) spectrophotometers. Chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the $CHCl_3$ peak at 7.24 ppm used as a standard).

^{13}C NMR spectra were determined on a Varian XL-300 (75 MHz) spectrophotometer. Chemical shifts are reported in parts per million (δ), relative to tetramethylsilane (with the central peak of $CDCl_3$ at 77.0 ppm used as a standard). Ultraviolet-visible spectra were recorded with a Perkin-Elmer 552 UV-vis spectrophotometer, and absorptions are reported in nanometers (nm).

High resolution mass spectra (HRMS) were measured on a Finnegan MATT-8200 spectrometer.

Elemental analyses were performed by Robertson Microlit Laboratories, Inc., of Madison, New Jersey.

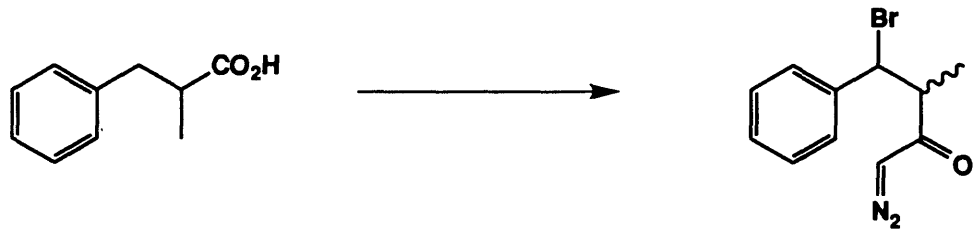


4-Bromo-1-diazo-4-phenyl-2-butanone (229).

A 250-mL, three-necked, round-bottomed flask equipped with a glass stopper, gas dispersion tube attached to a cylinder of HBr, and a gas outlet adaptor attached to a trap filled with water was charged with cinnamic acid (3.50 g, 23.6 mmol), 20 g of activated silica gel, and 120 mL of dichloromethane. HBr was bubbled through the reaction mixture for 20 min, and then the gas inlet and outlet were replaced by glass stoppers. The orange suspension was stirred at room temperature for 26 h and then was filtered with the aid of 250 mL of diethyl ether. The filtrate was washed with two 200-mL portions of water and 200 mL of brine, dried over magnesium sulfate, filtered, and concentrated to provide 4.70 g of 3-bromo-3-phenylpropionic acid as a white solid.

A 200-mL, one-necked, recovery flask equipped with a reflux condenser and argon inlet adaptor was charged with the crude acid, oxalyl chloride (3.59 g, 2.4 mL, 28.3 mmol), and 60 mL of benzene. As the suspension was heated to 65 °C, the solid acid dissolved and vigorous gas evolution began. After 30 min, gas evolution had ceased, and the reaction mixture was stirred for an additional 15.5 h at 65 °C. After this time, the reaction was allowed to cool to room temperature and was concentrated to a volume of ca. 10 mL. A 500-mL one-necked, round-bottomed flask (note: *clearseal joint*) was charged with a solution of CH_2N_2 (ca. 67 mmol, generated from diazald (20.24 g, 94.5mmol)) in 300 mL of diethyl ether. The yellow solution was cooled to 0 °C and stirred rapidly while the benzene solution of the acid chloride prepared above was added *via* pipette over 1 min (the flask containing the acid chloride was rinsed with two 5-mL portions of diethyl ether). The ice bath was removed after 10 min, stirring was stopped,

and the reaction mixture was allowed to warm to room temperature. After 1 h, the reaction mixture was concentrated to provide 5.10 g of a yellow oil. Column chromatography on 80 g of silica gel (compound applied adsorbed on 9 g of silica gel, elution with 20% ethyl acetate-hexanes) afforded 3.53g (60% from cinnamic acid) of pure 4-bromo-1-diazo-4-phenyl-2-butanone as a yellow solid with spectral data consistent with that previously reported for this compound.[121]



4-Bromo-1-diazo-3-methyl-4-phenyl-2-butanone (250).

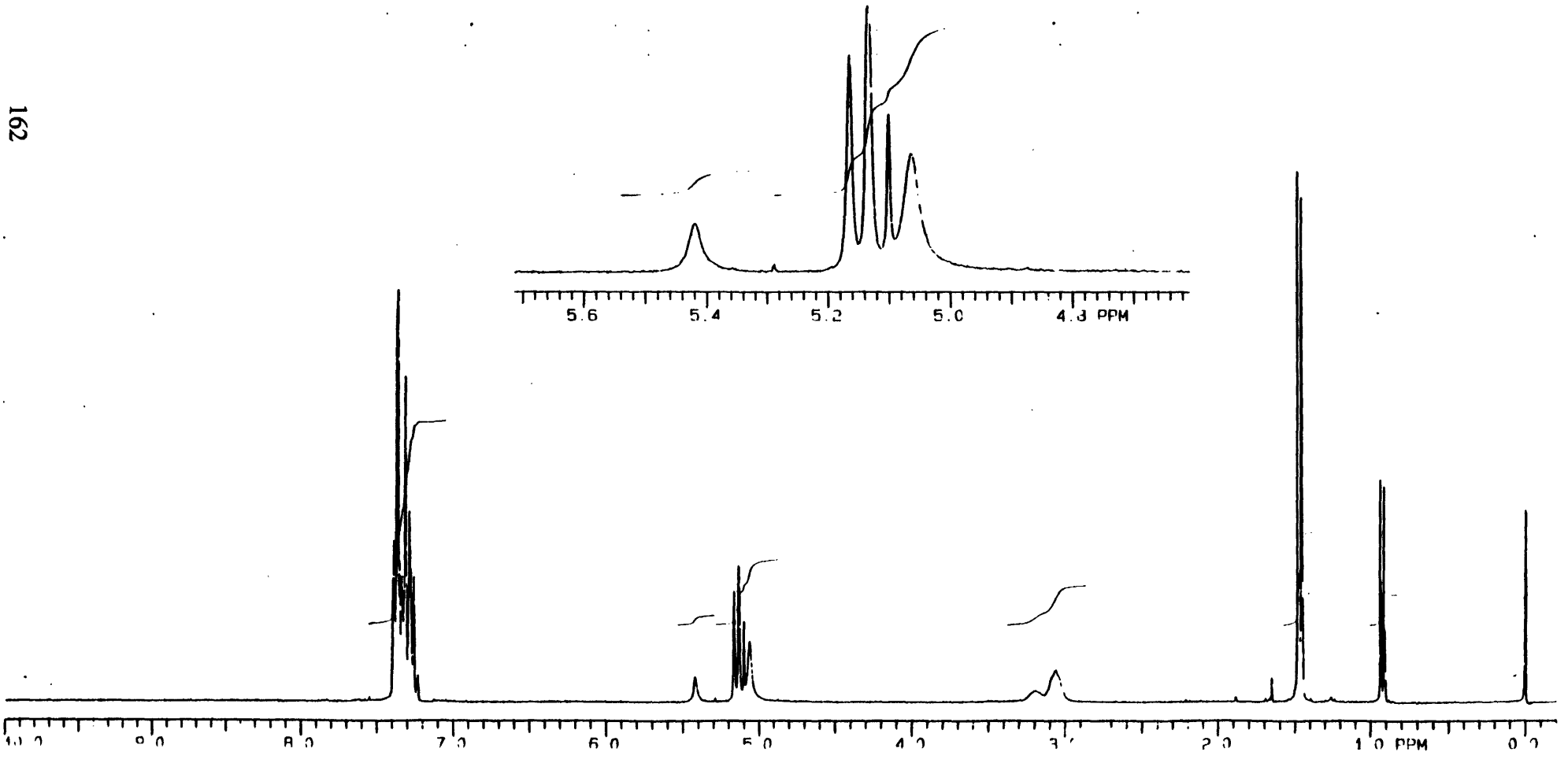
A 250-mL, three-necked, round-bottomed flask equipped with an argon inlet adaptor, reflux condenser, and a glass stopper was charged with 2-methyl-3-phenylpropionic acid[214] (2.00 g, 12.2 mmol), N-bromosuccimide (2.60 g, 14.6 mmol), and 60 mL of carbon tetrachloride. The suspension was heated to 80 °C while being irradiated with a sunlamp. After 2 h, the yellow reaction mixture was filtered hot, and the filtrate was allowed to cool to room temperature. The cooled solution was then refiltered and concentrated to provide 3.21 g of 3-bromo-2-methyl-3-phenylpropionic acid as a light brown solid.

A 200-mL, one-necked, recovery flask equipped with a reflux condenser and argon inlet adaptor was charged with the crude acid, oxalyl chloride (1.86 g, 1.30 mL, 14.6 mmol), and 60 mL of benzene. As the suspension was heated to 65 °C, vigorous gas evolution began. After 30 min, gas evolution had ceased, and the reaction mixture was stirred for an additional 15.5 h at 65 °C. After this time, the reaction was allowed to cool to room temperature and was concentrated to a volume of ca. 10 mL. A 500-mL one-necked, round-bottomed flask (note: *clearseal joint*) was charged with a solution of CH_2N_2 (ca. 35 mmol, generated from diazald (10.4 g, 48.8 mmol)) in 150 mL of diethyl ether. The yellow solution was cooled to 0 °C and stirred rapidly while the benzene solution of the acid chloride prepared above was added *via* pipette over 1 min (the flask containing the acid chloride was rinsed with two 5-mL portions of diethyl ether). The ice bath was removed

[214]This material was produced in 52% yield by alkylation of ethyl propionate (LDA, THF, benzyl bromide) followed by ester hydrolysis (KOH, H_2O). For a previous synthesis of this compound, see Brunner, H.; Leitner, W. *J. Organomet. Chem* **1990**, *387*, 209.

after 10 min, stirring was stopped, and the reaction mixture was allowed to warm to room temperature. After 2 h, the reaction mixture was concentrated to provide 3.57 g of a yellow oil. Column chromatography on 60 g of silica gel (compound applied adsorbed on 8 g of silica gel, elution with 20% ethyl acetate-hexanes) afforded 1.96 g (60% from 2-methyl-3-phenylproionic acid) of 4-bromo-1-diazo-3-methyl-4-phenyl-2-butanone as a yellow solid, mp = 51.0-61.0 °C (mixture of diastereomers).

^{1}H NMR (300 MHz, $CDCl_3$) :	7.22-7.39 (m, 5H), 5.42 (br s, 1H, minor isomer), 5.14 (app t, J = 8.8, 10.3 Hz, 1H), 5.06 (br s, 1H, major isomer), 3.03-3.11 (m, 1H), 1.47 (d, J = 7.1 Hz, 3H, major isomer), and 0.92 (d, J = 7.0 Hz, 3H, minor isomer).
^{13}C NMR (75 MHz, $CDCl_3$) :	195.4, 194.3, 140.5, 139.4, 128.8, 128.4, 127.8, 127.6, 57.5, 55.1, 55.0, 54.1, 52.8, 17.7, and 17.0.
IR (CCl_4) :	2890, 2080, 1635, 1535, 1440, 1345, 1245, 1195, 1130, and 990 cm^{-1}.
UV (CH_3CN) :	247 (ε = 20,145) and 192 (35,500) nm.
HRMS (EI) :	Calculated for $C_{11}H_{11}BrN_2O$: 266.0055 Found : 266.0048.


5.6
5.4
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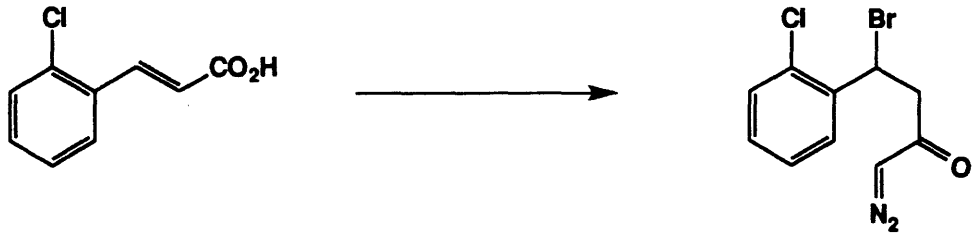


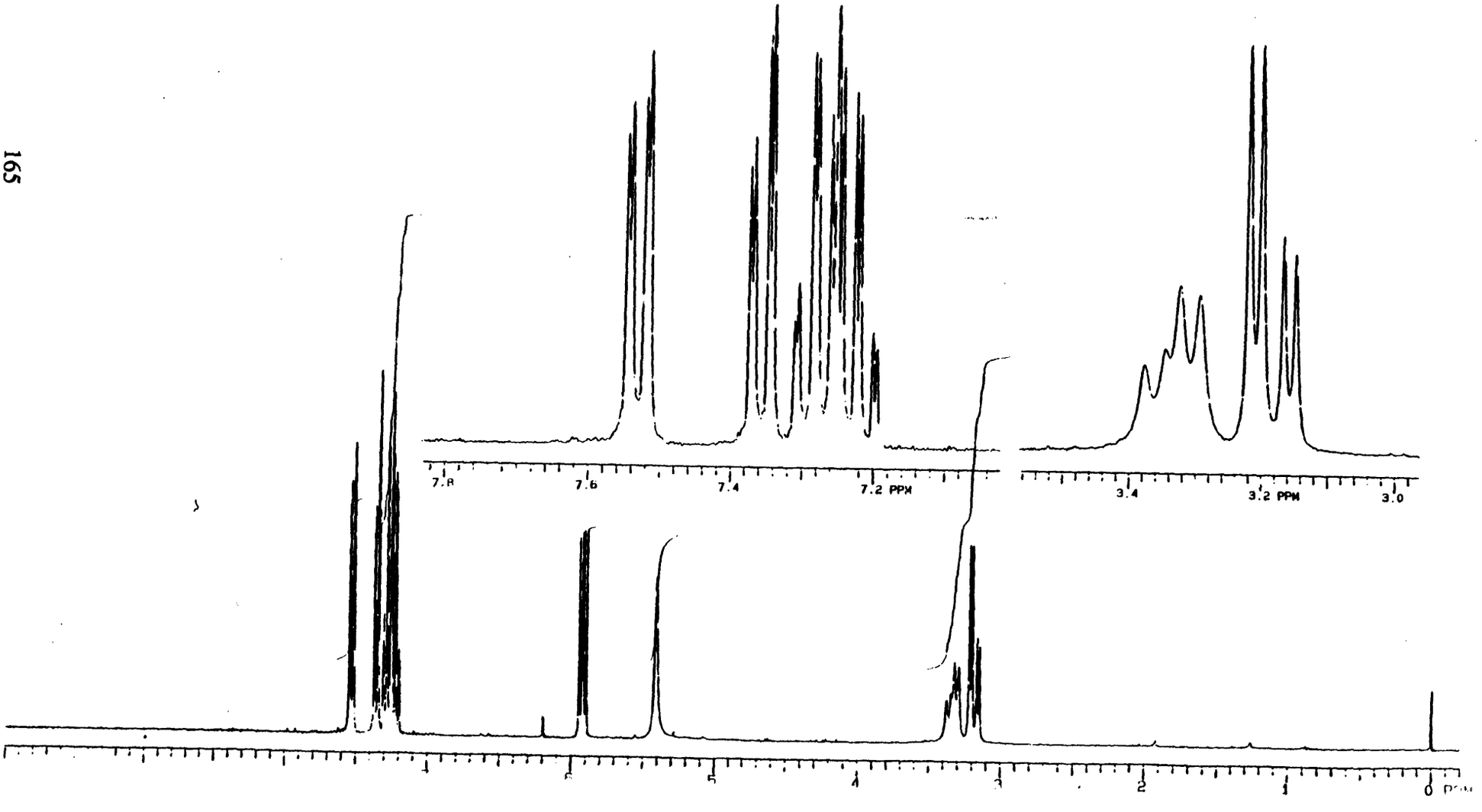
4-Bromo-4-(2-chlorophenyl)-1-diazo-2-butanone (234).

A 250-mL, three-necked, round-bottomed flask equipped with a glass stopper, gas dispersion tube attached to a cylinder of HBr, and a gas outlet adaptor attached to a trap filled with water was charged with 2-chlorocinnamic acid (2.06 g, 11.3 mmol), 20 g of activated silica gel, and 120 mL of dichloromethane. HBr was bubbled through the reaction mixture for 20 min, and then the gas inlet and outlet were replaced by glass stoppers. After 24 h, an additional 10 g of silica gel was added, and HBr was bubbled through the reaction mixture for 10 min. At t = 48 h, 20 mL of dichloromethane were added, followed by another 10 min of HBr. 48 Hours later, HBr was passed through the orange suspension for 10 min. After a total of 144 h, the reaction mixture (containing ca. 5% starting material as judged by ^{1}H NMR) was filtered with the aid of 250 mL of diethyl ether. The filtrate was washed with two 200-mL portions of water and 200 mL of brine, dried over magnesium sulfate, filtered, and concentrated to provide 2.23 g of 3-bromo-3-(2-chlorophenyl)propionic acid as an off-white solid.

A 200-mL, one-necked, recovery flask equipped with a reflux condenser and argon inlet adaptor was charged with the crude acid, oxalyl chloride (1.29 g, 0.870 mL, 10.2 mmol), and 40 mL of benzene. As the suspension was heated to 65 °C, the solid acid dissolved and vigorous gas evolution began. After 30 min, gas evolution had ceased, and the reaction mixture was stirred for an additional 15.5 h at 65 °C. After this time, the reaction was allowed to cool to room temperature and was concentrated to a volume of ca. 10 mL. A 500-mL one-necked, round-bottomed flask (note: *clearseal joint*) was charged

with a solution of CH_2N_2 (ca. 26 mmol, generated from diazald (7.75 g, 36.2 mmol)) in 125 mL of diethyl ether. The yellow solution was cooled to 0 °C and stirred rapidly while the benzene solution of the acid chloride prepared above was added *via* pipette over 1 min (the flask containing the acid chloride was rinsed with two 10-mL portions of diethyl ether). The ice bath was removed after 10 min, stirring was stopped, and the reaction mixture was allowed to warm to room temperature. After 2 h, the reaction mixture was concentrated to provide 2.88 g of a yellow oil. Column chromatography on 70 g of silica gel (compound applied adsorbed on 8 g of silica gel, elution with 20% ethyl acetate-hexanes) afforded 1.66 g (51% from 2-chlorocinnamic acid) of pure 4-bromo-4-(2-chlorophenyl)-1-diazo-2-butanone as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) :	7.53 (dd, J = 1.8, 7.6 Hz, 1 H), 7.35 (dd, J = 1.8, 7.6 Hz, 1 H), 7.19-7.31 (m, 2 H), 5.92 (dd, J = 5.7, 9.0 Hz, 1 H), 5.41 (br s, 1 H), and 3.26 (ABX, J_{ax} = 9.0 Hz, J_{bx} =5.7 Hz, J_{ab} = 15.7 Hz, δ_a = 3.34, δ_b = 3.18, 2 H).
^{13}C NMR (75 MHz, $CDCl_3$) :	189.6, 137.8, 132.7, 129.9, 129.7, 128.4, 127.4, 55.7, 48.5, and 43.5.
IR (thin film) :	3030, 2050, 1600, 1445, 1415, 1350, 1310, 1205, 1105, 1070, 1015, 1005, 915, 890, and 725 cm^{-1}.
UV max (CH_3CN) :	243 (ε = 13,050) and 195 (24,600) nm.
HRMS (EI) :	Calculated for $C_{10}H_8BrClN_2O$: 285.9509. Found : 285.9511.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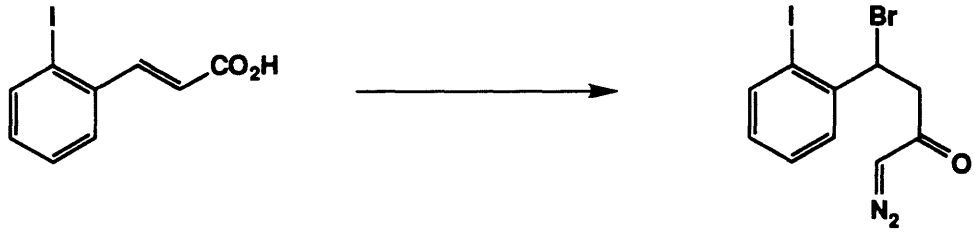


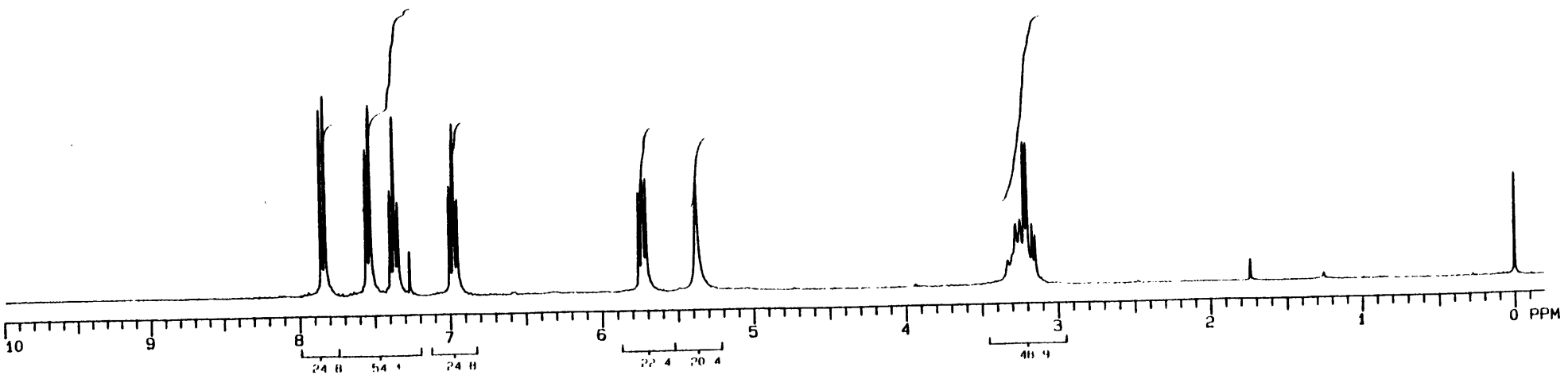
4-Bromo-4-(2-iodophenyl)-1-diazo-2-butanone (236).

A 500-mL, three-necked, round-bottomed flask equipped with a glass stopper, gas dispersion tube attached to a cylinder of HBr, and a gas outlet adaptor attached to a trap filled with water was charged with 2-iodocinnamic acid (5.00 g, 18.2 mmol), 60 g of activated silica gel, and 250 mL of dichloromethane. HBr was bubbled through the reaction mixture for 20 min, and then the gas inlet and outlet were replaced by glass stoppers. After 20 h, an additional 10 g of silica gel was added, and HBr was bubbled through the reaction mixture for 15 min. At t = 48 h, HBr was passed through the orange suspension for 10 min. After a total of 96 h, the reaction mixture was filtered with the aid of 500 mL of ethyl acetate. The filtrate was washed with two 500-mL portions of water and 500 mL of brine, dried over magnesium sulfate, filtered, and concentrated to provide 5.39 g of 3-bromo-3-(2-iodophenyl)propionic acid as an off-white oily solid.

A 200-mL, one-necked, recovery flask equipped with a reflux condenser and argon inlet adaptor was charged with the crude acid, oxalyl chloride (2.31 g, 1.60 mL, 18.2 mmol), and 50 mL of benzene. As the suspension was heated to 65 °C, the solid acid dissolved and vigorous gas evolution began. After 30 min, gas evolution had ceased, and the reaction mixture was stirred for an additional 14.5 h at 65 °C. After this time, the reaction was allowed to cool to room temperature and was concentrated to a volume of ca. 5 mL. A 500-mL one-necked, round-bottomed flask (note: *clearseal joint*) was charged with a solution of CH_2N_2 (ca. 43 mmol, generated from diazald (13.0 g, 60.7 mmol)) in 125 mL of diethyl ether. The yellow solution was cooled to 0 °C and stirred rapidly while the benzene solution

of the acid chloride prepared above was added *via* pipette over 1 min (the flask containing the acid chloride was rinsed with two 10-mL portions of diethyl ether). The ice bath was removed after 10 min, stirring was stopped, and the reaction mixture was allowed to warm to room temperature. After 2 h, the reaction mixture was concentrated to provide 5.81 g of a yellow oil. Column chromatography on 100 g of silica gel (compound applied adsorbed on 10 g of silica gel, elution with 20% ethyl acetate-hexanes) afforded 3.67 g (53% from 2-iodocinnamic acid) of pure 4-bromo-4-(2-iodophenyl)-1-diazo-2-butanone as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) :	7.84 (dd, J = 1.1, 7.9 Hz, 1 H), 7.54 (dd, J = 1.5, 7.9 Hz, 1 H), 7.37 (app t, J = 7.3, 7.9 Hz, 1H), 6.98 (dt, J = 1.5, 7.7 Hz, 1H), 5.73 (dd, J = 5.8, 8.8 Hz, 1H), 5.38, (br s, 1H), and 3.15-3.35 (m, 2H).
^{13}C NMR (75 MHz, $CDCl_3$) :	189.4, 142.6, 140.0, 130.2, 129.0, 128.0, 99.4, 55.8, 52.0, and 49.2.
IR (thin film) :	3095, 2100, 1620, 1460, 1430, 1375, 1340, 1130, 1090, 1010, 940, 910, and 750 cm^{-1}.
UV max (CH_3CN) :	351 (ε = 300), 350 (205) and 218 (20,690) nm.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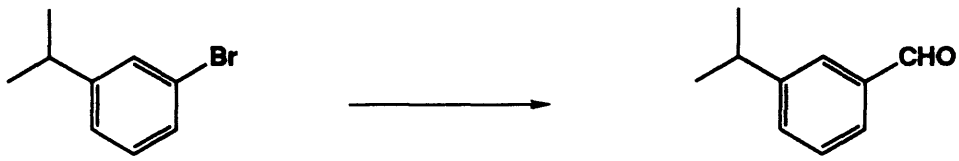
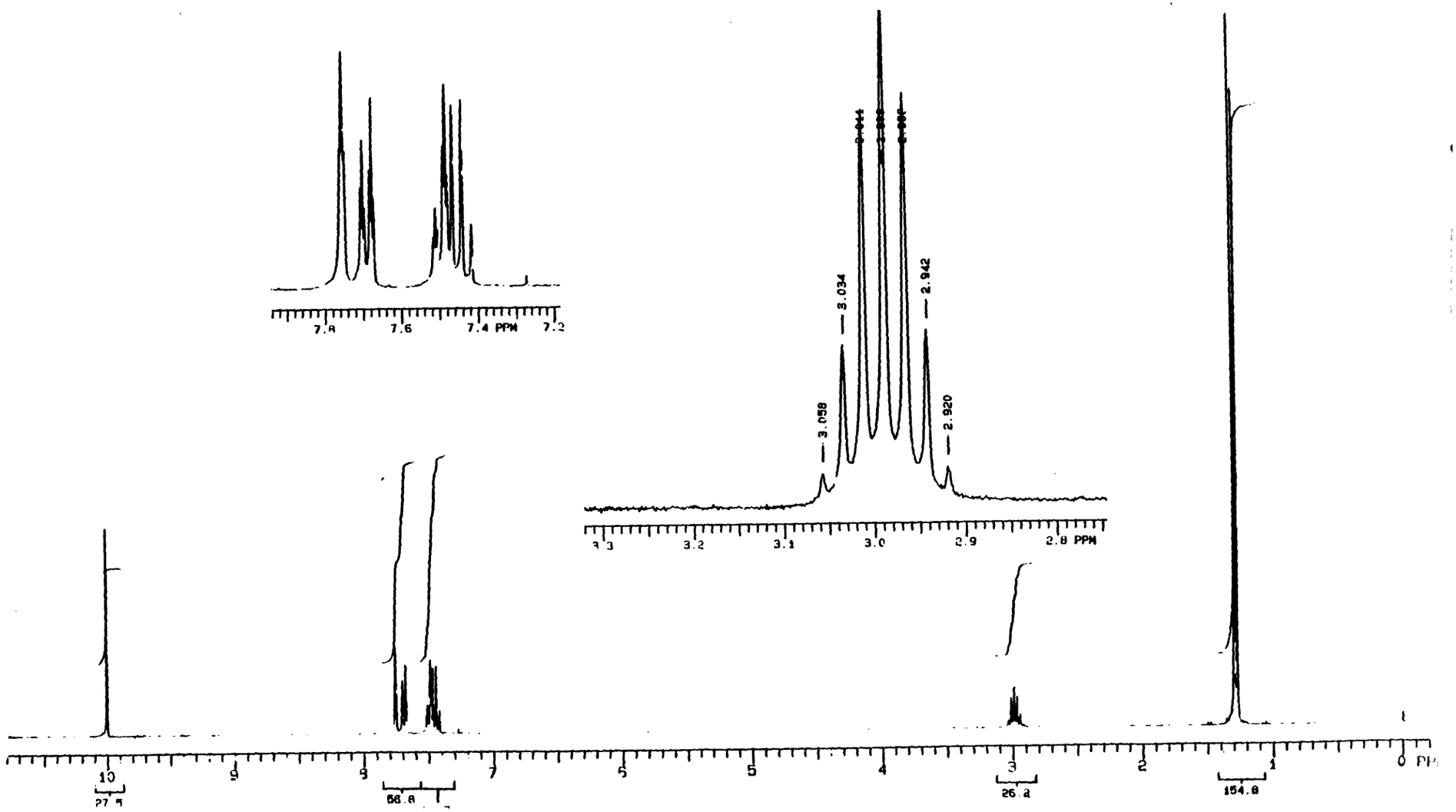


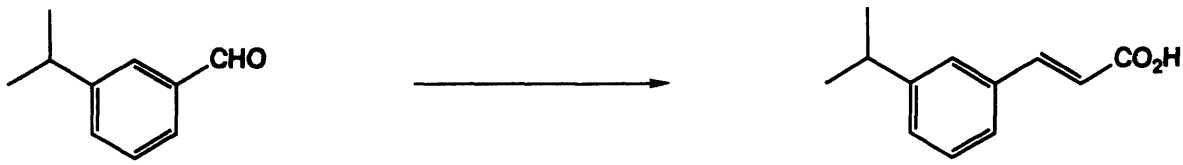
3-Isopropylbenzaldehyde (325).

A 250-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and an argon inlet adaptor was charged with *n*-BuLi (2.47 M in hexanes, 11.2 mL, 27.6 mmol) and 65 mL of THF, and the resulting yellow-colored solution was cooled to -78 °C in a dry ice-acetone bath. A 25-mL, one-necked, pear-shaped flask was charged with 3-bromocumene (5.00 g, 25.1 mmol) and 10 mL of THF. The bromide solution was transferred dropwise via cannula to the *n*-BuLi solution over 15 min, and the flask was rinsed with 5 mL of THF. The orange reaction mixture was stirred at -78 °C for 30 min, and then DMF (2.20 g, 2.30 mL, 30.1 mmol) was added via syringe in one portion. The resulting light yellow solution was stirred at -78 °C for 45 min and then poured into a 250-mL Erlenmeyer flask containing 20 mL of conc HCl and 50 mL of water. The mixture was stirred rapidly for 30 min and then transferred to a separatory funnel. The aqueous phase was extracted with 50 mL of diethyl ether, and the combined organic phases were washed with 50 mL of saturated sodium bicarbonate solution and 50 mL of brine, dried over magnesium sulfate, filtered, and concentrated to provide 3.94 g of a yellow oil. This material was used without further purification in the next reaction. The product of another run (2.40 g) was purified by column chromatography on 80 g of silica gel (elution with 5% ethyl acetate-hexanes) to afford 1.93 g (87%) of pure 3-isopropylbenzaldehyde.[168]

^{1}H NMR (300 MHz, $CDCl_3$) :	10.00 (s, 1H), 7.75 (t, J = 1.8 Hz, 1H), 7.71-7.67 (m, 1H), 7.68-7.42 (m, 2H), 2.99 (septet, J = 7.0 Hz, 1H), and1.28 (d, J = 7.0 Hz, 6H).
^{13}C NMR (75 MHz, $CDCl_3$) :	192.5, 149.8, 136.5, 132.8, 128.9, 127.6, 127.2, 33.8, and 23.7.

IR (CCl_4) : 2980, 2940, 2880, 2820, 2740, 1705, 1605, 1465, 1390, 1370, 1340, 1310, 1280, 1245, 1180, 1170, 1145, 1080, 1050, 1000, 905, 860, 800, 755, 710, and 700 cm^{-1}.


7.8
7.6
7.4 PPM
7.2
3.058
3.034
2.942
2.920
3.3
3.2
3.1
3.0
2.9
2.8 PPM
10
9
8
7
6
5
4
3
2
1
0 PPM
27.5
56.8
26.2
154.8

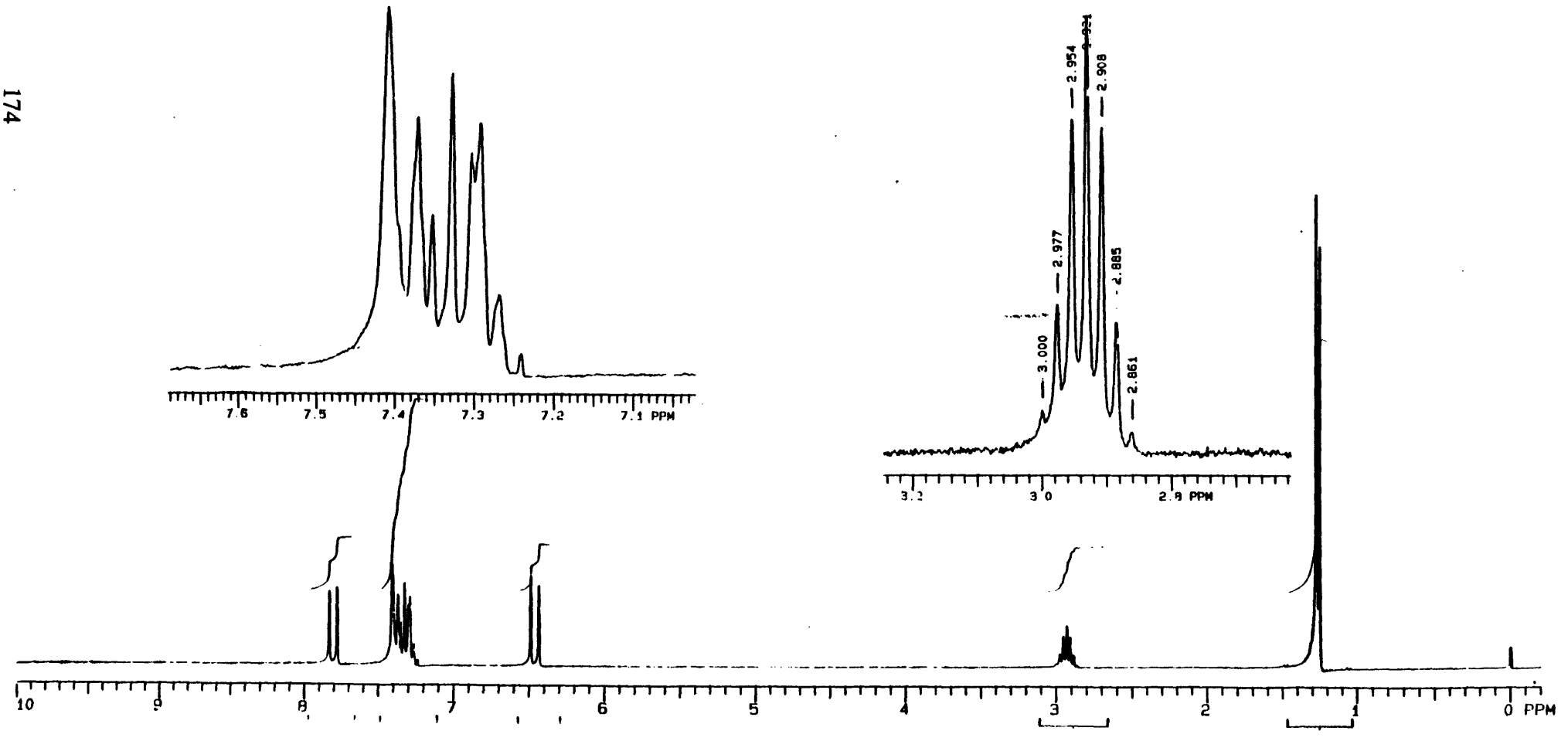


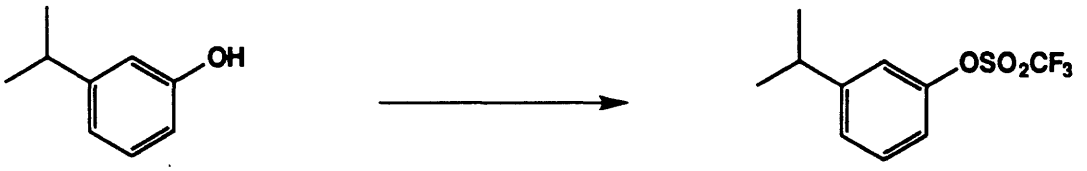
3-Isopropylcinnamic acid (237).

A 250-mL, one-necked, round-bottomed flask equipped with an argon inlet adaptor and reflux condenser was charged with 3-isopropylbenzaldehyde (3.94 g) and 30 mL of pyridine. Malonic acid (5.23 g, 50.2 mmol) was added, and the mixture was stirred until all the acid had dissolved (ca. 5 min). Piperidine (4.28 g, 5.00 mL, 50.2 mmol) was added in one portion via syringe, and the reaction mixture was heated to 130 °C. After 16 h, the orange reaction mixture was allowed to cool to room temperature and poured into a 250-mL Erlenmeyer flask containing 20 mL of conc HCl and 50 g of ice. The yellow suspension was extracted with three 50-mL portions of ether, and the combined organic phases were back-extracted with three 50-mL portions of aqueous 10% sodium hydroxide solution. The combined aqueous phases were acidified to pH 1 with conc HCl, and the acidic suspension was extracted with three 50-mL portions of ether. The combined organic phases were washed with two 50-mL portions of brine, dried over magnesium sulfate, filtered, and concentrated to provide 4.03 g of a tan solid. This material was used without further purification in the next reaction. A small portion of the crude product from another run was recrystallized from aqueous ethanol to afford pure 3-isopropylcinnamic acid as a white solid, mp 72.0-73.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) :	7.81 (d, J = 16.0 Hz, 1H), 7.41-7.29 (m, 4H), 6.46 (d, J = 16.0 Hz, 1H), 2.93 (sept, J = 7.0 Hz, 1H), and 1.27 (d, J = 7.0 Hz, 6H).
^{13}C NMR (75 MHz, $CDCl_3$) :	172.8, 149.6, 147.4, 133.9, 129.0, 128.9, 126.5, 125.8, 116.9, 33.9, and 23.8.

IR (CCl_4) :	2970, 2690, 2600, 1690, 1630, 1580, 1565, 1480, 1465, 1365, 1310, 1280, 1230, 1205, 1190, 985, 940, 870, and 690 cm^{-1}.
UV-Vis max (hexane) :	276 (ε = 29,400).


7.6
7.5
7.4
7.3
7.2
7.1 PPM
3.000
2.977
2.954
2.908
2.885
2.861
3.2
3.0
2.8 PPM
10
9
8
7
6
5
4
3
2
1
0 PPM

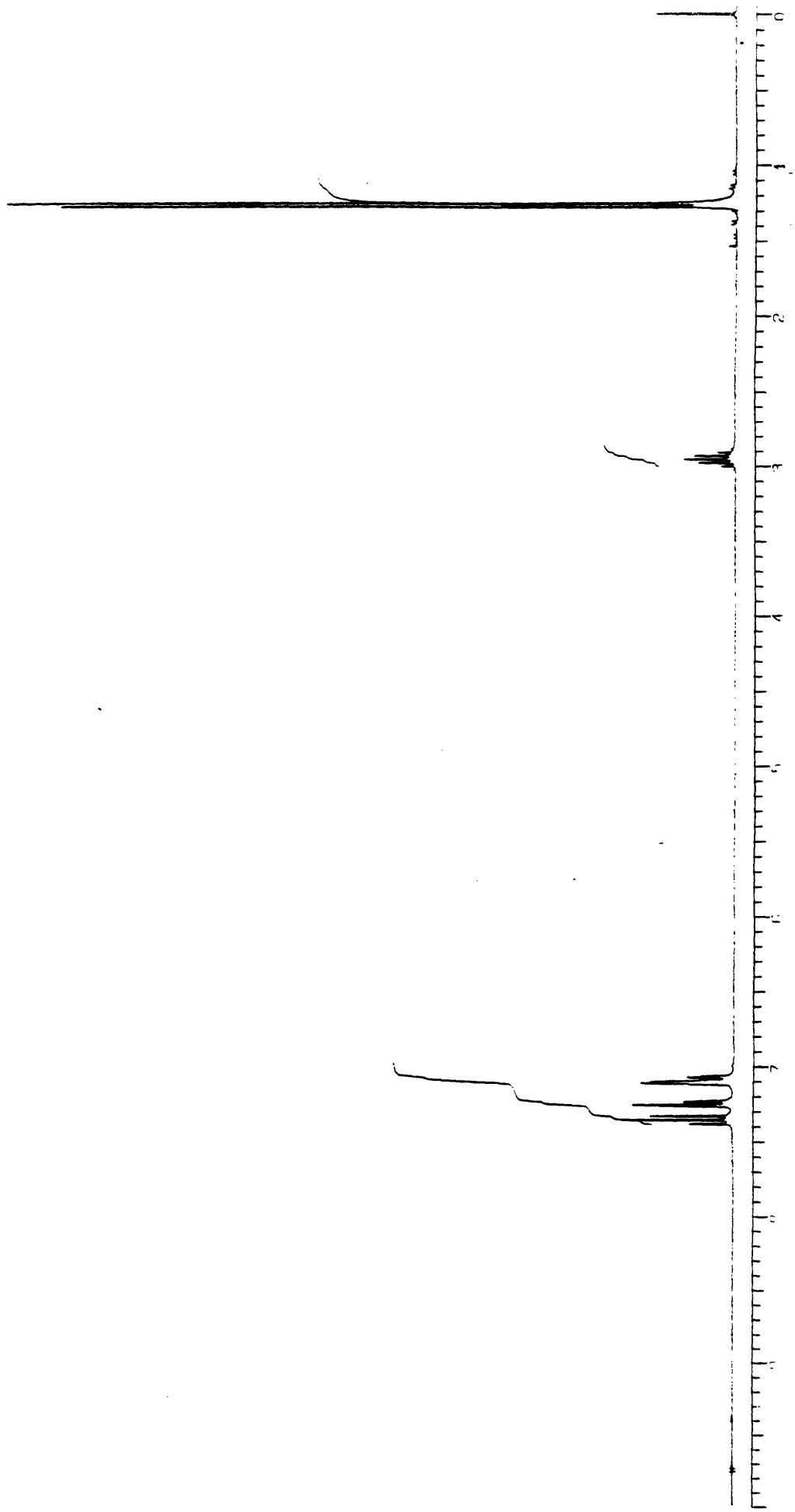


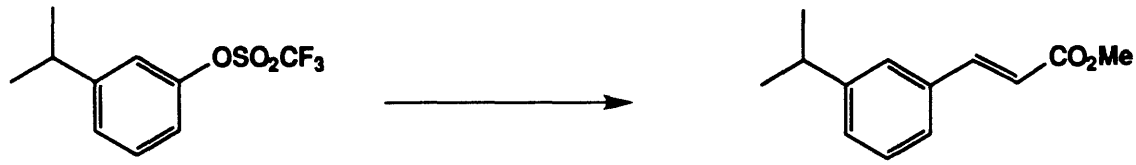
3-Isopropylphenyl triflate (328).

A 250-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and an argon inlet adaptor was charged with 4-dimethylaminopyridine (5.54 g, 45.4 mmol) and 100 mL of dichloromethane. The resulting solution was cooled to -20 °C in a dry ice-acetone bath and stirred for 5 min. 3-Isopropylphenol (3.86 g, 3.9 mL, 28.4 mmol) was added dropwise over 2 min. After 5 min, the reaction mixture was treated dropwise with triflic anhydride (10.0 g, 5.9 mL, 35.4 mmol) over 10 min. The cooling bath was then removed and the resulting thick white suspension was allowed to warm to room temperture over 2 h. The reaction mixture was then poured into 200 mL of water and the phases were separated. The organic phase was washed with two 100-mL portions of water and 100 mL of brine, dried over magnesium sulfate, filtered, and concentrated to provide 7.89 g of a yellow oil. This material was used without further purification in the next reaction.

The product of another run (7.89 g) was purified by column chromatography on 40 g of silica gel (elution with hexanes) to afford 7.48 g (98%) of pure 3-isopropylphenyl triflate.

^{1}H NMR (300 MHz, $CDCl_3$) :	7.36 (t, J = 7.7 Hz, 1H), 7.23-7.26 (m, 1H), 7.06-7.11 (m, 2H), 2.95 (sept, J = 6.8 Hz, 1H), and 1.40 (d, J = 6.8 Hz, 6H).
^{13}C NMR (75 MHz, $CDCl_3$) :	151.8, 149.6, 129.9, 126.4, 120.8, 119.2, 118.4, 34.0, and 23.8.
IR (thin film) :	2960, 2920, 2860, 1610, 1580, 1485, 1425, 1365, 1335, 1280, 1210, 1145, 1110, 1050, 935, 880, 810, 790, 765, and 695 cm^{-1}.





Methyl 3-isopropylcinnamate.

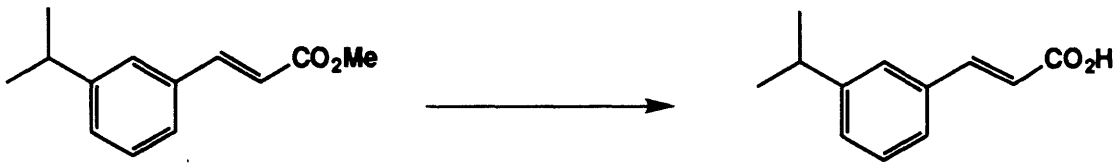
A 250-mL, three-necked, round-bottomed flask equipped with a rubber septum, reflux condenser, and an argon inlet adaptor was charged with 3-isopropylphenyl triflate (7.61 g, 28.4 mmol), 1,3-bis(diphenylphosphino) propane (1.17 g, 2.84 mmol), triethylamine (3.46 g, 4.8 mL, 34.2 mmol), palladium acetate (0.636 g, 2.84 mmol), and 100 mL of dimethylsulfoxide. The reaction miture was stirred to dissolve most of the solids and then methyl acrylate (12.2 g, 12.8 mL, 141 mmol) was added in one portion. The reaction mixture was then heated to 120 °C. After 16 h, the reaction mixture was allowed to cool to room temperature and was poured into 600 mL of water. The resulting solution was extracted with four 100-mL portions of diethyl ether. The combined organic phases were washed with two 200-mL portions of 5% HCl solution and 300 mL of brine, dried over magnesium sulfate, filtered, and concetrated to provide 5.79 g of a yellow oil. This material was used without further purification in the next reaction.

The product of another run (2.95 g) was purified by column chromatography on 45 g of silica gel (elution with 5% ethyl acetate-hexanes, compound applied adsorbed on 5 g of silica gel) to afford 2.18 g (92%) of pure methyl 3-isopropylcinnamate as a clear oil.

^{1}H NMR (300 MHz, $CDCl_3$) :	7.70 (d, J = 15.9 Hz, 1H), 7.22-7.37 (m, 4 H), 6.44 (d, J = 15.9 Hz, 1H), 3.80 (s, 3H), 2.91 (sept, J = 6.9 Hz, 1H), and 1.26 (d, J = 6.9 Hz, 6H).
^{13}C NMR (75 MHz, $CDCl_3$) :	167.2, 149.3, 145.0, 134.1, 128.7, 128.4, 126.1, 125.4, 117.3, 51.6, 34.0, and 23.9.

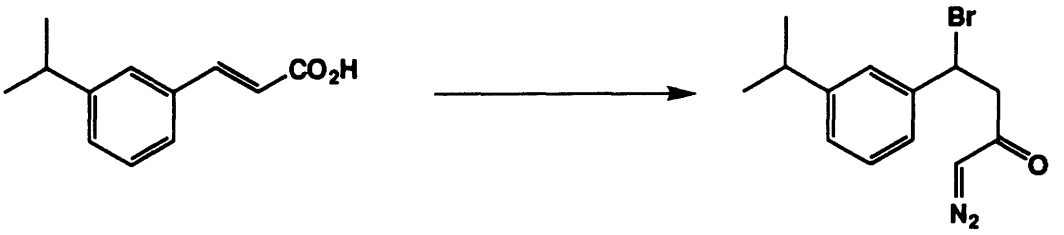
IR (thin film) : 2960, 1715, 1635, 1580, 1435, 1365, 1270, 1220, 1165, 1035, 1010, 980, 855, 790, and 685 cm^{-1}.

PPM
101.9
17.3
56.1
16.1
16.2
16.4



3-Isopropylcinnamic acid (237).

A 200-mL recovery flask equipped with an argon inlet adaptor was charged with methyl 3-isopropylcinnamate (9.41 g), 130 mL of methanol, and 30 mL of water. The cloudy suspension was cooled to 0 °C in an ice bath while lithium hydroxide hydrate (10.2 g, 243 mmol) was added in one portion. After 6 h, an additonal portion of the $LiOH{\cdot}H_2O$ was added (4.00 g, 95.3 mmol) to the reaction mixture. After 12 h, the reaction mixture was acidified with conc HCl, and the acidic solution was extracted with four 80-mL portions of dichloromethane. The combined organic phases were back-extracted with three 100-mL portions of saturated sodium bicarbonate solution, and the combined aqueous phases were acidified to pH 1 with conc HCl. The acidic solution was then extracted with three 85-mL portions of diethyl ether, and the combined organic phases were washed with 200 mL of brine, dried over magnesium sulfate, filtered, and concentrated to provide 8.41 g of a 3-isopropylcinnamic acid as a white solid with spectral data indistinguishable from the material prepared by the reaction of 3-isopropylbenzaldehyde with malonic acid.



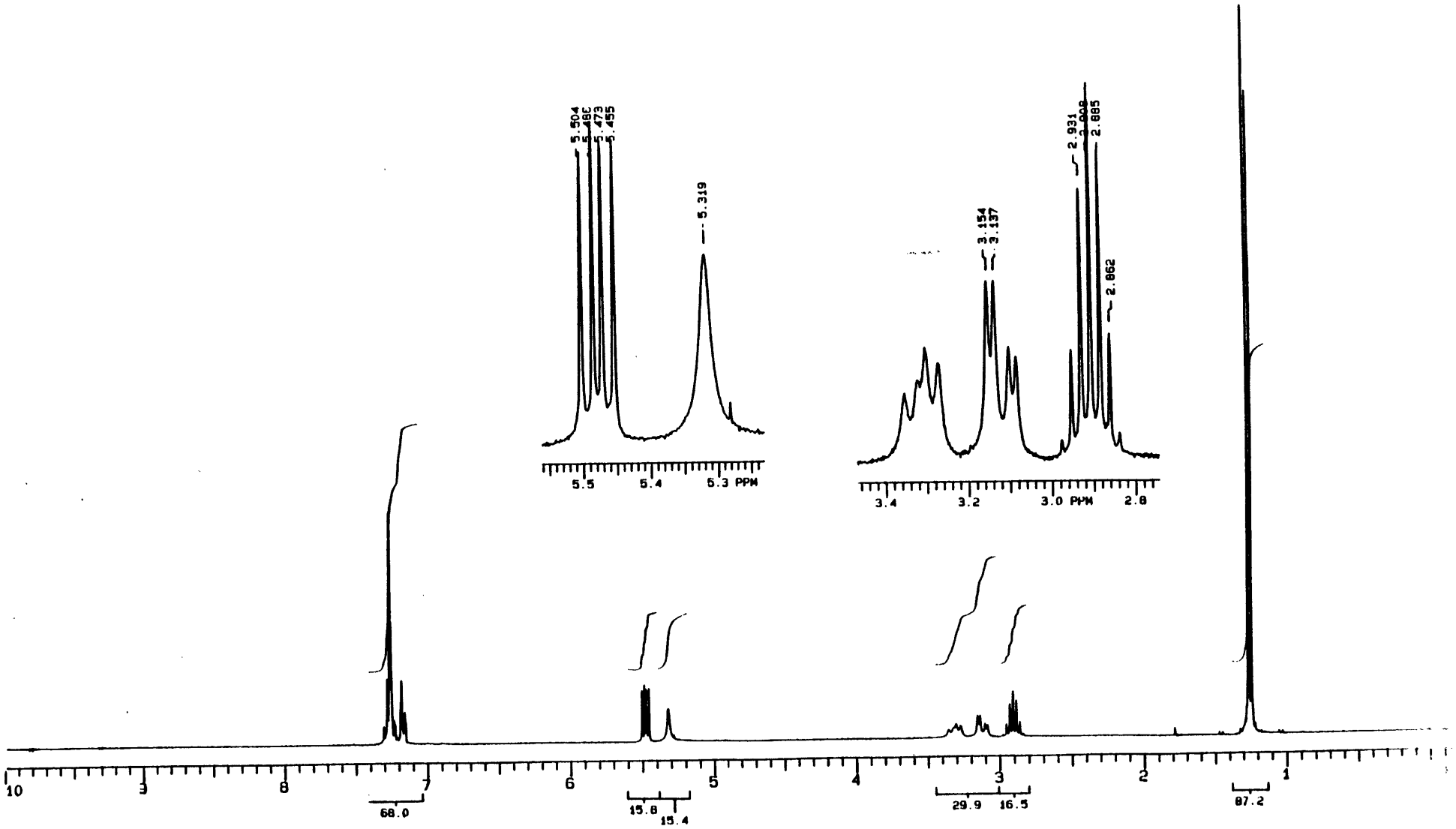
4-Bromo-1-diazo-4-(3-isopropylphenyl)-2-butanone (238).

A 250-mL, three-necked, round-bottomed flask equipped with a glass stopper, gas dispersion tube attached to a cylinder of HBr, and a gas outlet adaptor attached to a trap filled with water was charged with 3-isopropylcinnamic acid (4.03 g), 20 g of activated silica gel, and 120 mL of dichloromethane. HBr was bubbled through the reaction mixture for 20 min, and then the gas inlet and outlet adaptors were replaced by glass stoppers. The orange suspension was stirred at room temperature for 23 h and then filtered with the aid of 150 mL of diethyl ether. The filtrate was washed with two 150-mL portions of water and 150 mL of brine, dried over magnesium sulfate, filtered, and concentrated to provide 4.98 g of a yellow brown oil.

A 200-mL, one-necked, recovery flask equipped with a reflux condensor and an argon inlet adaptor was charged with the crude acid, oxalyl chloride (3.23 g, 2.20 mL, 25.4 mmol), and 40 mL of benzene. As the solution was heated to 70 °C, vigorous gas evolution began. After 30 min, gas evolution had ceased, and the reaction mixture was stirred for an additional 13.5 h at 70 °C. After this time, the reaction mixture was allowed to cool to room temperature and was concentrated to a volume of ca. 10 mL. A 500-mL, one-necked, round-bottomed flask (note: *clearseal joint*) was charged with a solution of CH_2N_2 (ca. 62 mmol, generated from diazald (18.8 g, 87.4 mmol)) in 250 mL of diethyl ether. The yellow solution was cooled to 0 °C and rapidly stirred while the benzene solution of acid chloride prepared above was added by pipette over 1 min (the flask containing the acid chloride was rinsed with two 5-mL portions of diethyl ether). The ice bath was removed, stirring was stopped, and the reaction mixture was allowed to

warm to room temperature. After 3 h, the reaction mixture was concentrated to provide 7.20 g of a yellow oil. Column chromatography on 140 g of silica gel (compound applied adsorbed on 15 g silica gel, elution with 20% ethyl acetate-hexanes) afforded 3.74 g (51% from 3-bromocumene) of pure 4-bromo-1-diazo-4-(3-isopropylphenyl)-2-butanone as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) :	7.28-7.16 (m, 4H), 5.48 (dd, J = 5.3, 9.3 Hz, 1H), 5.32 (br s, 1H), 3.22 (ABX, J_{ax} = 9.3 Hz, J_{bx} = 5.2 Hz, J_{ab} = 10.3 Hz, δ_a = 3.32, δ_b= 3.12, 2H), 2.91 (sept, J = 6.9 Hz, 1H), and 1.25 (d, J = 6.9 Hz, 6H).
^{13}C NMR (75 MHz, $CDCl_3$) :	190.2, 149.4, 140.7, 128.7, 126.7, 125.3, 124.5, 55.8, 50.0, 48.6, 33.9, and 23.8.
IR (thin film) :	3100, 2960, 2925, 2870, 2100, 1635, 1485, 1460, 1380, 1350, 1330, 1240, 1160, 1135, 1100, 795, and 700 cm^{-1}.
UV-Vis max (CH_3CN) :	246 (ε = 28,425) and 197 (71,920) nm.
HRMS (FAB) :	Calculated for $C_{13}H_{15}BrN_2O$ $(M+H)^+$: 295.0446. Found: 295.0445.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2.885
2.862
3.4
3.2
3.0 PPM
2.8
10
9
8
7
6
5
4
3
2
1
68.0
15.8
15.4
29.9
16.5
87.2

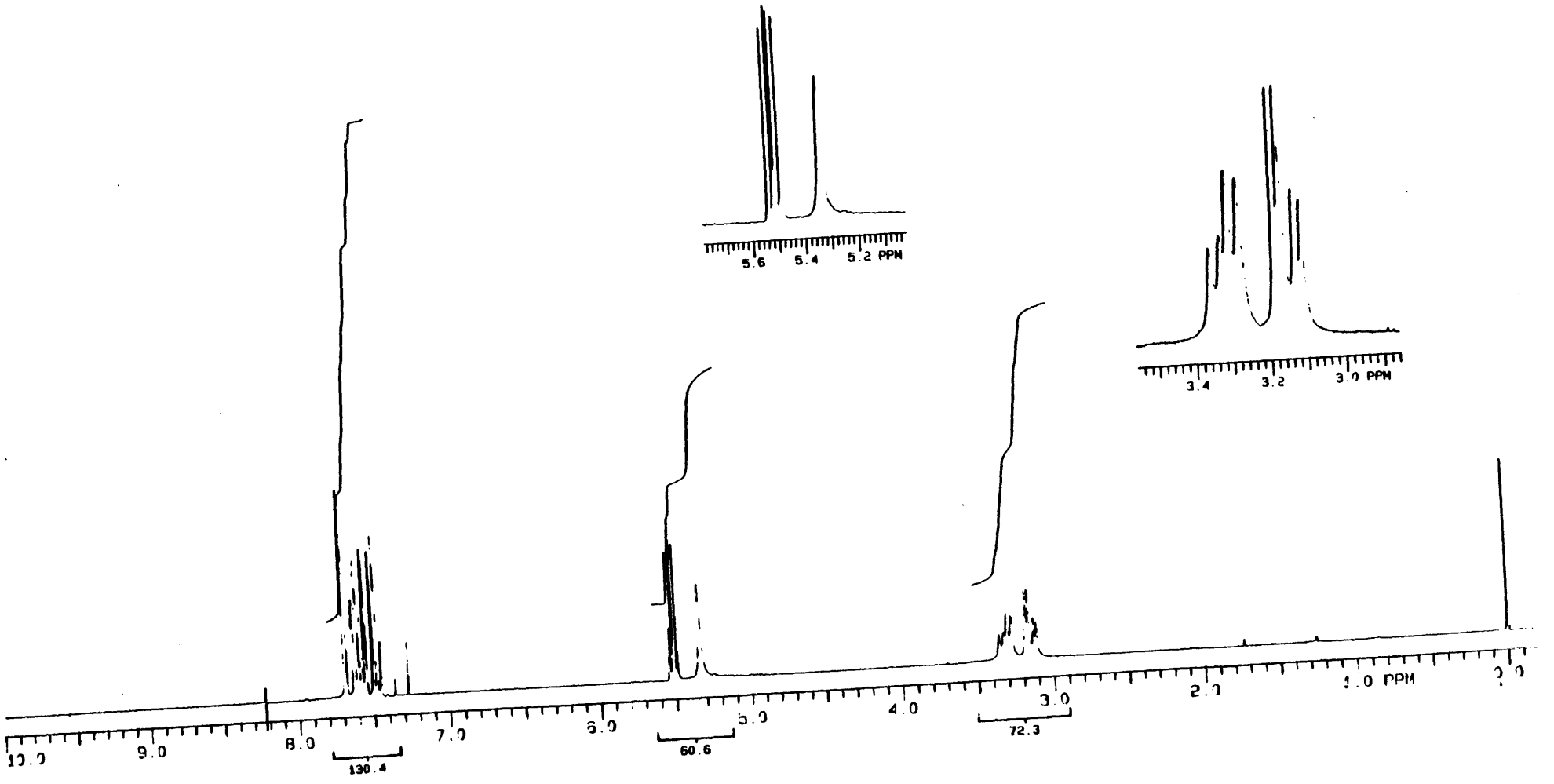
4-Bromo-4-(3-bromophenyl)-2-butanone (240).

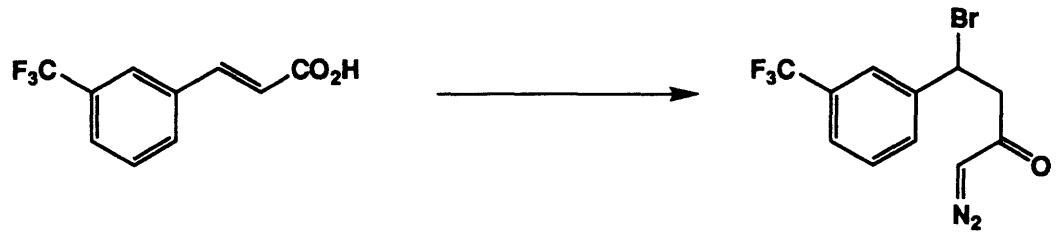
A 250-mL, three-necked, round-bottomed flask equipped with a glass stopper, gas dispersion tube attached to a cylinder of HBr, and a gas outlet adaptor attached to a trap filled with water was charged with 3-bromocinnamic acid (3.00 g, 13.2 mmol), 30 g of activated silica gel, and 150 mL of dichloromethane. HBr was bubbled through the reaction mixture for 20 min, and then the gas inlet and outlet were replaced by glass stoppers. After 48 h, 10 g of silica gel was added, and the reaction mixture was treated with HBr for 10 min, followed by two additional treatements with HBr (10 min each) after 72 h and 96 h. After a total of 120 h, the reaction mixture (containg ca. 9% starting material as judged by ^{1}H NMR) was filtered with the aid of 250 mL of diethyl ether. The filtrate was washed with two 200-mL portions of water and 200 mL of brine, dried over magnesium sulfate, filtered, and concentrated to provide 3.31 g of 3-bromo-3-(3-bromophenyl)propionic acid as a brown oil.

A 200-mL, one-necked, recovery flask equipped with a reflux condenser and argon inlet adaptor was charged with the crude acid, oxalyl chloride (1.64 g, 1.10 mL, 12.9 mmol), and 50 mL of benzene. As the suspension was heated to 65 °C, vigorous gas evolution began. After 30 min, gas evolution had ceased, and the reaction mixture was stirred for an additional 11.5 h at 65 °C. After this time, the reaction was allowed to cool to room temperature and was concentrated to a volume of ca. 10 mL. A 500-mL one-necked, round-bottomed flask (note: *clearseal joint*) was charged with a solution of CH_2N_2 (ca. 33 mmol, generated from diazald (10.0 g, 46.7 mmol)) in 150 mL of diethyl ether. The yellow

solution was cooled to 0 °C and stirred rapidly while the benzene solution of the acid chloride prepared above was added *via* pipette over 1 min (the flask containing the acid chloride was rinsed with two 5-mL portions of diethyl ether). The ice bath was removed after 10 min, stirring was stopped, and the reaction mixture was allowed to warm to room temperature. After 1 h, the reaction mixture was concentrated to provide 3.75 g of a yellow oil. Column chromatography on 60 g of silica gel (compound applied adsorbed on 8 g of silica gel, elution with 20% ethyl acetate-hexanes) afforded 2.42 g (55% from 3-bromocinnamic acid) of pure 4-bromo-4-(3-bromophenyl)-1-diazo-2-butanone as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) :	7.68 (s, 1H), 7.45-7.63 (m, 3H), 5.51 (dd, J = 8.9, 6.0 Hz, 1H), 5.34 (br s, 1H), and 3.23 (ABX, J_{ax} = 8.9 Hz, J_{bx} = 6.0 Hz, J_{ab} = 15.8 Hz, δ_a = 3.31, δ_b = 3.14, 2H).	
^{13}C NMR (75 MHz, $CDCl_3$) :	189.6, 143.1, 131.8, 130.3 (2 peaks), 126.0, 122.7, 56.0, 49.8, and 46.5.	
IR (thin film) :	3090, 2100, 1635, 1590, 1570, 1465, 1425, 1375, 1335, 1230, 1160, 1125, 1070, 1025, 990, 945, 915, 780, and 745 cm^{-1}.	
UV (CH_3CN) :	351 (ε = 730) and 205 (27,490) nm.	
HRMS (EI) :	Calculated for $C_{10}H_8Br_2N_2O$:	330.9081.
	Found:	330.9078.


5.6
5.4
5.2 PPM
3.4
3.2
3.0 PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0 PPM
130.4
60.6
72.3



4-Bromo-1-diazo-4-(3-(trifluoromethyl)phenyl)-2-butanone (242).

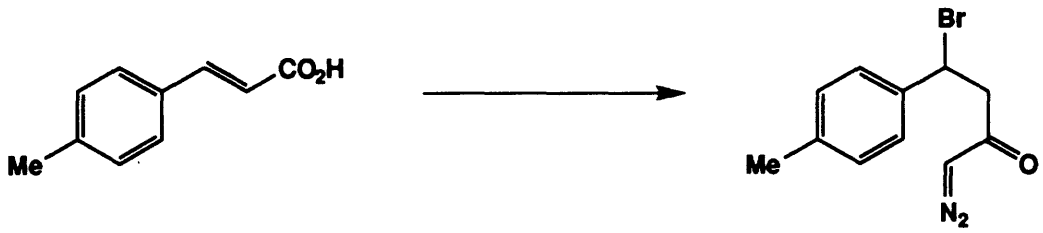
A 250-mL, three-necked, round-bottomed flask equipped with a glass stopper, gas dispersion tube attached to a cylinder of HBr, and a gas outlet adaptor attached to a trap filled with water was charged with 3-(trifluoromethyl)cinnamic acid (3.00 g, 13.9 mmol), 50 g of activated silica gel, and 220 mL of dichloromethane. HBr was bubbled through the reaction mixture for 20 min, and then the gas inlet and outlet were replaced by glass stoppers. After 168 h, 30 mL of dichloromethane was added, and HBr was bubbled through the reaction mixture for 20 min. At t = 192 h, the reaction mixture was filtered with the aid of 200 mL of diethyl ether and concentrated to give an orange oil. The crude acid (containing ca. 50% starting material as judged by ^{1}H NMR) was subjected to the original reaction conditions (30 g of silica gel, 150 mL of dichloromethane, 20 min of HBr), and after a total of 360 h, the reaction mixture (containing ca. 21% starting material as judged by ^{1}H NMR) was filtered with the aid of 150 mL of diethyl ether. The filtrate was washed with two 150-mL portions of water and 150 mL of brine, dried over magnesium sulfate, filtered, and concentrated to provide 2.10 g of 3-bromo-3-(3-(trifluoromethyl)phenyl)propionic acid as a brown oil.

A 200-mL, one-necked, recovery flask equipped with a reflux condenser and argon inlet adaptor was charged with the crude acid, oxalyl chloride (1.08 g, 0.720 mL, 8.48 mmol), and 40 mL of benzene. As the suspension was heated to 65 °C, vigorous gas evolution began. After 30 min, gas evolution had ceased, and the reaction mixture was stirred for an additional 14.5 h at 65 °C. After this time, the reaction was allowed to cool to room temperature and was concentrated to a volume of ca. 10 mL. A 500-mL one-necked,

round-bottomed flask (note: *clearseal joint*) was charged with a solution of CH_2N_2 (ca. 25 mmol, generated from diazald (7.57 g, 35.4 mmol)) in 150 mL of diethyl ether. The yellow solution was cooled to 0 °C and stirred rapidly while the benzene solution of the acid chloride prepared above was added *via* pipette over 1 min (the flask containing the acid chloride was rinsed with two 5-mL portions of diethyl ether). The ice bath was removed after 10 min, stirring was stopped, and the reaction mixture was allowed to warm to room temperature. After 1 h, the reaction mixture was concentrated to provide 2.45 g of a yellow oil. Column chromatography on 60 g of silica gel (compound applied adsorbed on 5 g of silica gel, elution with 20% ethyl acetate-hexanes) afforded 1.34 g (30% from 3-(trifluoromethyl)cinnamic acid) of pure 4-bromo-1-diazo-4-(3-(trifluoromethyl)phenyl)-2-butanone as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) :	7.68 (s, 1H), 7.27-7.63 (m, 3H), 5.51 (dd, J = 8.7, 5.9 Hz, 1H), 5.33 (br s, 1H), and 3.21 (ABX, J_{ax} = 8.7 Hz, J_{bx} = 5.9 Hz, J_{ab} = 15.7 Hz, δ_a = 3.29, δ_b = 3.12, 2H).
^{13}C NMR (75 MHz, $CDCl_3$) :	189.5, 142.0, 130.7, 129.4, 125.5, 125.4, 124.1, 124.0, 55.9, 49.7, and 46.4.
IR (thin film) :	3090, 2100, 1625, 1485, 1440, 1370, 1330, 1230, 1160, 1120, 1070, 1025, 895, 800, 790, and 750 cm^{-1}.
UV (CH_3CN) :	352 (ε = 570), 243 (11,500), and 205 (19,190) nm.
HRMS (EI) :	Calculated for $C_{11}H_8BrF_3N_2O$: 320.9850. Found: 320.9853.

65.3
62.7
131.6
3.4
5.5 5.4 5.3 5.2 PPM

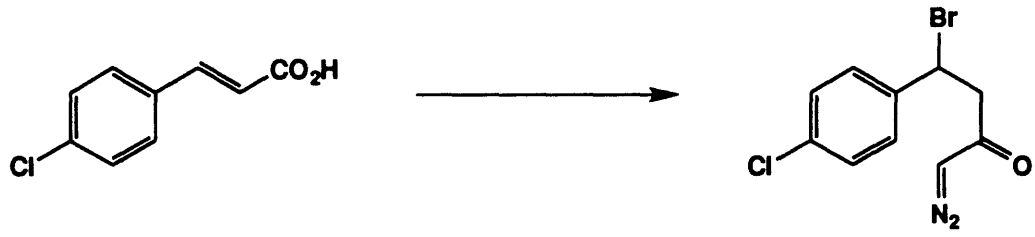


4-Bromo-1-diazo-4-(4-methylphenyl)-2-butanone (244).

A 100-mL, three-necked, round-bottomed flask equipped with a glass stopper, gas dispersion tube attached to a cylinder of HBr, and a gas outlet adaptor attached to a trap filled with water was charged with 4-methylcinnamic acid (2.00 g, 12.3 mmol), 7 g of activated silica gel, and 40 mL of dichloromethane. HBr was bubbled through the reaction mixture for 20 min, and then the gas inlet and outlet were replaced by glass stoppers. The orange suspension was stirred at room temperature for 22 h and then was filtered with the aid of 200 mL of diethyl ether. The filtrate was washed with three 50-mL portions of water and 50 mL of brine, dried over magnesium sulfate, filtered, and concentrated to provide 2.58 g of 3-bromo-3-(4-methylphenyl)propionic acid as a white solid.

A 250-mL, one-necked, round-bottomed flask equipped with a reflux condenser and argon inlet adaptor was charged with the crude acid, oxalyl chloride (2.35 g, 1.60 mL, 18.5 mmol), and 40 mL of benzene. As the suspension was heated to 70 °C, the solid acid dissolved and vigorous gas evolution began. After 2 h, gas evolution had ceased, and the reaction mixture was stirred for an additional 16 h at 70 °C. After this time, the reaction was allowed to cool to room temperature and was concentrated to a volume of ca. 10 mL. A 500-mL one-necked, round-bottomed flask (note: *clearseal joint*) was charged with a solution of CH_2N_2 (ca. 35 mmol, generated from diazald (10.71 g, 50.00 mmol)) in 125 mL of diethyl ether. The yellow solution was cooled to 0 °C and stirred rapidly while the benzene solution of the acid chloride prepared above was added *via* addition funnel over 45

min. After 3 h, the reaction mixture was concentrated to provide 3.19 g of a yellow solid. Column chromatography on 100 g of silica gel (compound applied adsorbed on 10 g of silica gel, elution with 20% ethyl acetate-hexanes) afforded 1.55 g (47% from 4-methylcinnamic acid) of 4-bromo-1-diazo-4-(4-methylphenyl)-2-butanone as a yellow solid (approximately 75% pure by TLC analysis). This material was used without further purification in the ring expansion-annulation reaction (see pp 226).



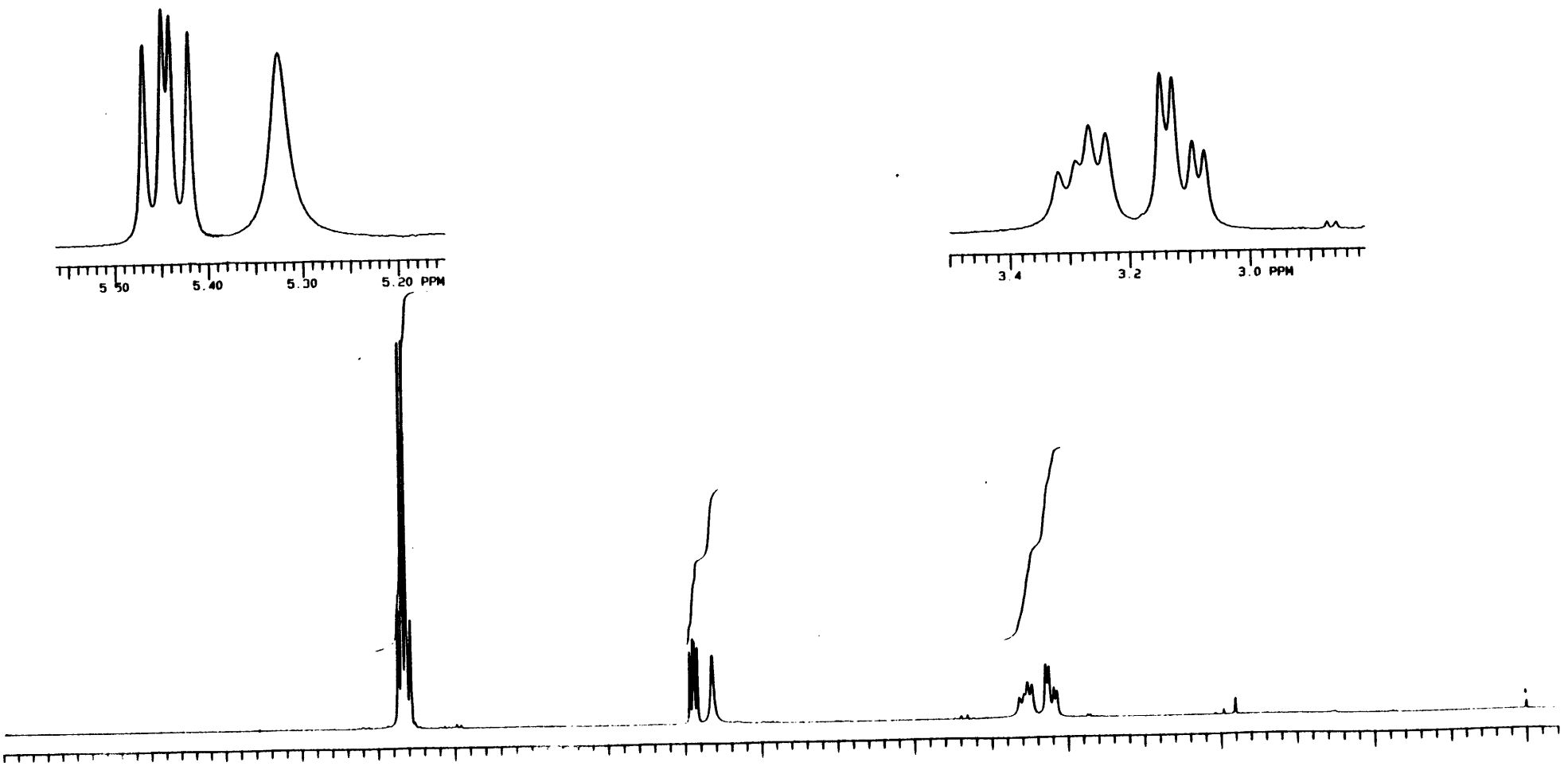
4-Bromo-4-(4-chlorophenyl)-1-diazo-2-butanone (246).

A 250-mL, three-necked, round-bottomed flask equipped with a glass stopper, gas dispersion tube attached to a cylinder of HBr, and a gas outlet adaptor attached to a trap filled with water was charged with 4-chlorocinnamic acid (3.00 g, 16.4 mmol), 30 g of activated silica gel, and 150 mL of dichloromethane. HBr was bubbled through the reaction mixture for 20 min, and then the gas inlet and outlet were replaced by glass stoppers. The orange suspension was stirred at room temperature for 48 h and then was filtered with the aid of 150 mL of diethyl ether and 100 mL of chloroform. The filtrate was washed with three 150-mL portions of water and 150 mL of brine, dried over magnesium sulfate, filtered, and concentrated to provide 3.54 g of 3-bromo-3-(4-chlorophenyl)propionic acid as a white solid.

A 200-mL, one-necked, recovery flask equipped with a reflux condenser and argon inlet adaptor was charged with the crude acid, oxalyl chloride (1.97 g, 1.30 mL, 15.5 mmol), and 40 mL of benzene. As the suspension was heated to 65 °C, the solid acid dissolved and vigorous gas evolution began. After 30 min, gas evolution had ceased, and the reaction mixture was stirred for an additional 15.5 h at 65 °C. After this time, the reaction was allowed to cool to room temperature and was concentrated to a volume of ca. 10 mL. A 500-mL one-necked, round-bottomed flask (note: *clearseal joint*) was charged with a solution of CH_2N_2 (ca. 35 mmol, generated from diazald (10.7 g, 50.0 mmol)) in 125 mL of diethyl ether. The yellow solution was cooled to 0 °C and stirred rapidly while the benzene solution of the acid chloride prepared above was added *via* pipette over 1 min (the flask

containing the acid chloride was rinsed with two 10-mL portions of diethyl ether). The ice bath was removed after 10 min, stirring was stopped, and the reaction mixture was allowed to warm to room temperature. After 2 h, the reaction mixture was concentrated to provide 3.89 g of a yellow oil. Column chromatography on 60 g of silica gel (compound applied adsorbed on 10 g of silica gel, elution with 20% ethyl acetate-hexanes) afforded 2.89 g (61% from 4-chlorocinnamic acid) of pure 4-bromo-4-(4-chlorophenyl)-1-diazo-2-butanone as a yellow solid, mp 76.5-78.5 °C.

^{1}H NMR (300 MHz, $CDCl_3$) :	7.38-7.26 (m, 4 H), 5.44 (dd, J = 6.1, 8.6 Hz, 1 H), 5.27 (br s, 1 H), and 3.19 (ABX, J_{ax} = 6.1 Hz, J_{bx} = 8.6 Hz, J_{ab} = 15.5 Hz, δ_a = 3.26, δ_b = 3.11, 2 H).
^{13}C NMR (75 MHz, $CDCl_3$) :	189.7, 139.4, 134.3, 128.9, 128.6, 55.8, 49.7, and 46.9.
IR (CCl_4) :	3110, 2910, 2110, 1645, 1545, 1490, 1410, 1370, 1240, 1130, 1090, and 1010 cm^{-1}.
UV max (CH_3CN):	242 (ε = 24,070) and 195 (40,600) nm.
HRMS (EI) :	Calculated for $C_{10}H_8BrClN_2O$: 285.9509. Found : 285.9516.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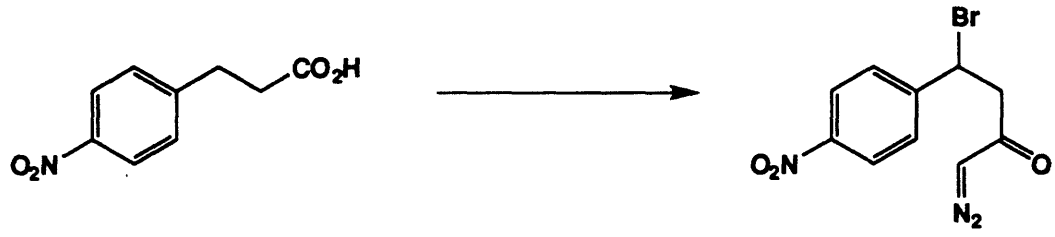
5.40
5.30
5.20 PPM
3.4
3.2
3.0 PPM



4-Bromo-1-diazo-4-(4-nitrophenyl)-2-butanone (252).

A 250-mL, one-necked, round-bottomed flask equipped with an argon inlet adaptor, reflux condenser, and a glass stopper was charged with 3-(4-nitrophenyl)propionic acid[215] (2.69 g, 13.8 mmol), *N*-bromosuccimide (2.94 g, 16.5 mmol), AIBN (ca. 0.020 g) and 80 mL of carbon tetrachloride. The suspension was heated to 80 °C while being irradiated with a sunlamp. After 4 h, the yellow reaction mixture was hot filtered. The cooled solution was diluted with 150 mL of dichloromethane and washed with two 100-mL portions of water and 100 mL of brine, dried over magnesium sulfate, filtered, and concentrated to provide 2.20 g of 3-bromo-3-(4-nitrophenyl)propionic acid as a yellow solid. This crude material was combined with the product of another run (0.854 g) and subjected to the reaction conditions outlined below.

A 200-mL, one-necked, recovery flask equipped with a reflux condenser and argon inlet adaptor was charged with the crude acid (3.05 g), oxalyl chloride (1.70 g, 1.10 mL, 13.4 mmol), and 80 mL of benzene. As the suspension was heated to 65 °C, vigorous gas evolution began. After 30 min, gas evolution had ceased, and the reaction mixture was stirred for an additional 14.5 h at 65 °C. After this time, the reaction was allowed to cool to room temperature and was concentrated to a volume of ca. 10 mL. A 500-mL one-necked, round-bottomed flask (note: *clearseal joint*) was charged with a solution of CH_2N_2 (ca. 32 mmol, generated from diazald (9.54 g, 44.5 mmol)) in 150 mL of diethyl ether. The yellow solution was cooled to 0 °C and stirred rapidly while the benzene solution of the acid

[215]This compound was prepared via nitration of hydrocinnamic acid (HNO_3, H_2SO_4). For a related preparation of this material, see: Walter, M.; Besendorf, H.; Schnider, O. *Helv. Chim. Acta* **1963**, *46*, 1127.

chloride prepared above was added *via* pipette over 1 min (the flask containing the acid chloride was rinsed with two 5-mL portions of diethyl ether). The ice bath was removed after 10 min, stirring was stopped, and the reaction mixture was allowed to warm to room temperature. After 1 h, the reaction mixture was concentrated to provide 2.76 g of a yellow oil. Column chromatography on 80 g of silica gel (compound applied adsorbed on 12 g of silica gel, elution with 33% ethyl acetate-hexanes) afforded 1.66 g (28% from 3-(4-nitrophenyl)proionic acid) of 4-bromo-1-diazo-4-(4-nitrophenyl)-2-butanone as a yellow solid, mp 92.0-93.5 °C.

^{1}H NMR (300 MHz, $CDCl_3$) :	8.20 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.8 Hz, 2H), 5.52 (dd, J = 8.2, 6.5 Hz, 1H), 5.36 (br s, 1H), and 3.26 (ABX, J_{ax} = 8.2 Hz, J_{bx} = 6.5 Hz, J_{ab} = 15.9 Hz, δ_a = 3.34, δ_b = 3.19, 2H).
^{13}C NMR (75 MHz, $CDCl_3$) :	189.0, 147.7, 147.5, 128.2, 123.9, 56.0, 49.4, and 45.4.
IR ($CDCl_3$) :	3100, 2100, 1630, 1600, 1520, 1365, 1345, 1125, 1000, and 850 cm^{-1}.
UV (CH_3CN) :	351 (ε = 895) and 272 (12,300) nm.
HRMS (EI) :	Calculated for $C_{10}H_8BrN_3O_3$: 296.9749. Found: 296.9746.

PPM
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10

4-Bromo-4-(4-cyanophenyl)-1-diazo-2-butanone (253).

A 100-mL, one-necked, round-bottomed flask equipped with an argon inlet adaptor, reflux condenser, and a glass stopper was charged with 3-(4-cyanophenyl)propionic acid[216] (0.917 g, 5.23 mmol), *N*-bromosuccimide (1.12 g, 6.28 mmol), AIBN (ca. 0.015g) and 40 mL of carbon tetrachloride. The suspension was heated to 80 °C while being irradiated with a sunlamp. After 2 h, the yellow reaction mixture was allowed to cool to room temperature. The cooled solution was diluted with 100 mL of dichloromethane and washed with two 100-mL portions of water and 100 mL of brine, dried over magnesium sulfate, filtered, and concentrated to provide 1.30 g of 3-bromo-3-(4-cyanophenyl)propionic acid as an off-white solid.

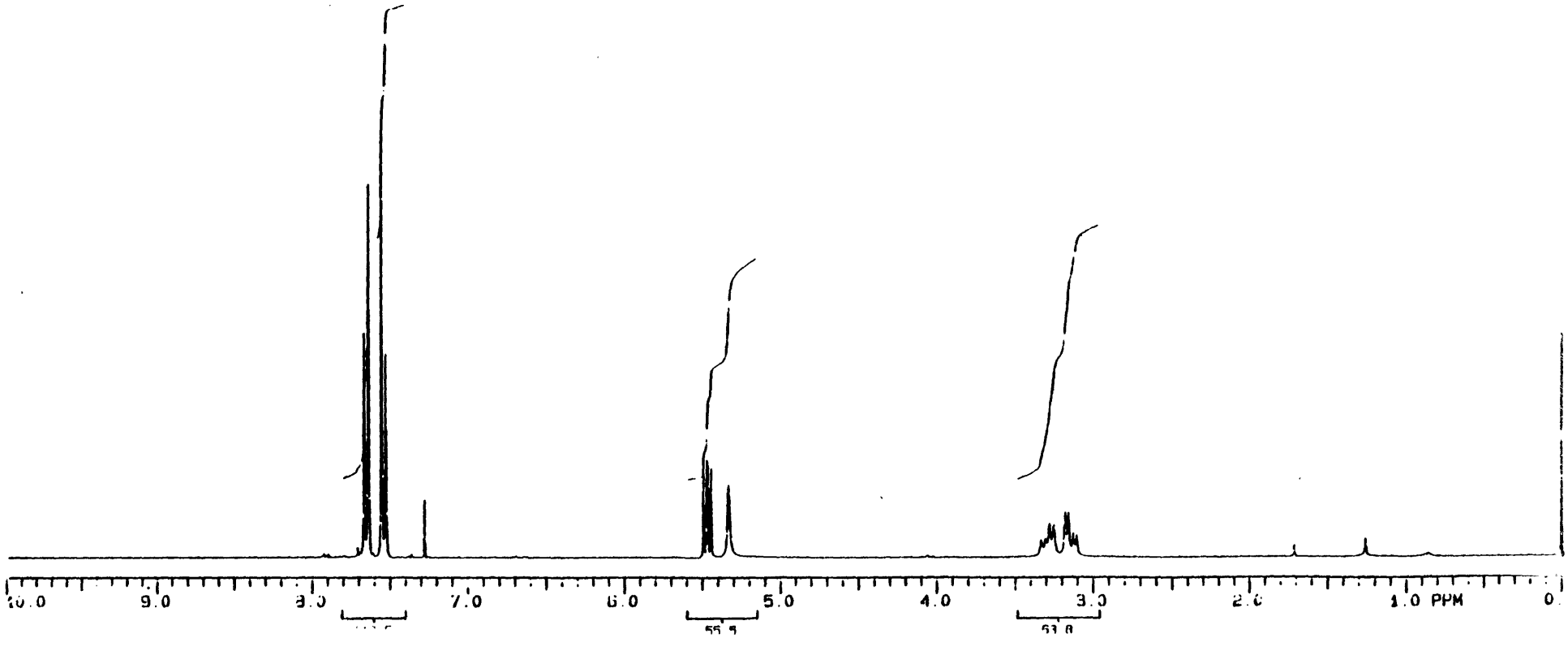
A 200-mL, one-necked, recovery flask equipped with a reflux condenser and argon inlet adaptor was charged with the crude acid, oxalyl chloride (0.797 g, 0.540 mL, 6.28 mmol), and 50 mL of benzene. As the suspension was heated to 65 °C, vigorous gas evolution began. After 30 min, gas evolution had ceased, and the reaction mixture was stirred for an additional 15.5 h at 65 °C. After this time, the reaction was allowed to cool to room temperature and was concentrated to a volume of ca. 10 mL. A 250-mL one-necked, round-bottomed flask (note: *clearseal joint*) was charged with a solution of CH_2N_2 (ca. 15 mmol, generated from diazald (4.49 g, 20.94 mmol)) in 100 mL of diethyl ether. The yellow solution was cooled to 0 °C and stirred rapidly while the benzene solution of the acid

[216]This material was produced in 77% yield by alkylation of *t*-butyl acetate (LDA, THF, α-iodo-*p*-tolunitrile) followed by hydrolysis of the *t*-butyl ester (TMSCl, NaI, CH_3CN). For a previous synthesis of this compound, see Wagner, G.; Garbe, C.; Richter, P. *Pharmazie* **1973**, *28*, 724.

chloride prepared above was added *via* pipette over 1 min (the flask containing the acid chloride was rinsed with two 5-mL portions of diethyl ether). The ice bath was removed after 10 min, stirring was stopped, and the reaction mixture was allowed to warm to room temperature. After 1 h, the reaction mixture was concentrated to provide 1.27 g of a yellow oil. Column chromatography on 60 g of silica gel (compound applied adsorbed on 8 g of silica gel, elution with 20% ethyl acetate-hexanes) afforded 0.599 g (41% from 3-(4-cyanophenyl)propionic acid) of 4-bromo-4-(4-cyanophenyl)-1-diazo-2-butanone as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) :	7.65 (d, J = 8.5 Hz, 2H), 7.54 (d, J = 8.5 Hz, 2H), 5.47 (dd, J = 8.2, 6.4 Hz, 1H), 5.33 (br s, 1H), and 3.22 (ABX, J_{ax} = 8.2 Hz, J_{bx} = 6.4 Hz, J_{ab} = 16.1 Hz, δ_a = 3.29, δ_b = 3.14, 2H).
^{13}C NMR (75 MHz, $CDCl_3$) :	189.2, 145.9, 132.6, 128.0, 118.2, 112.3, 55.9, 49.3, and 45.8.
IR (thin film) :	3090, 2980, 2200, 2080, 1610, 1585, 1400, 1350, 1295, 1220, 1120, 1080, 1005, 930, 900, 835, and 715 cm^{-1}.
UV (CH_3CN) :	352 (ε = 1,530), 243 (21,500), 194 (21,400) and 191 (21,500) nm.
HRMS (EI) :	Calculated for $C_{11}H_8BrN_3O$: 276.9851. Found: 276.9849.

200



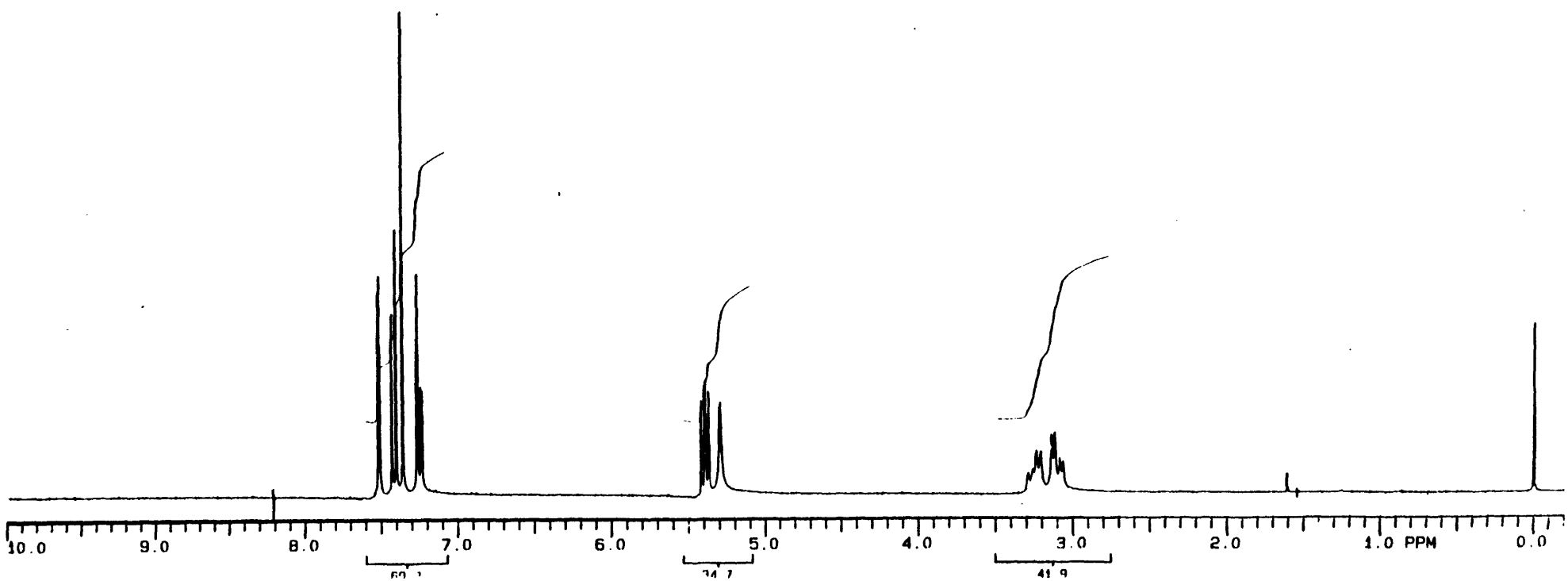
4-Bromo-1-diazo-4-(3,4-dichlorophenyl)-2-butanone (248).

A 250-mL, three-necked, round-bottomed flask equipped with a glass stopper, gas dispersion tube attached to a cylinder of HBr, and a gas outlet adaptor attached to a trap filled with water was charged with 3,4-dichlorocinnamic acid (2.00 g, 9.21 mmol), 20 g of activated silica gel, and 120 mL of dichloromethane. HBr was bubbled through the reaction mixture for 20 min, and then the gas inlet and outlet were replaced by glass stoppers. After 24 h, HBr was bubbled through the reaction mixture for 10 min. At t = 40 h, an additional 10 g of silica gel was added, followed by another 20 min of HBr. After a total of 90 h, the reaction mixture was filtered with the aid of 200 mL of diethyl ether. The filtrate was washed with two 150-mL portions of water and 150 mL of brine, dried over magnesium sulfate, filtered, and concentrated to provide 1.94 g of 3-bromo-3-(3,4-dichlorophenyl)propionic acid as an off-white solid.

A 200-mL, one-necked, recovery flask equipped with a reflux condenser and argon inlet adaptor was charged with the crude acid, oxalyl chloride (0.991 g, 0.670 mL, 7.81 mmol), and 50 mL of benzene. As the suspension was heated to 65 °C, the solid acid dissolved and vigorous gas evolution began. After 30 min, gas evolution had ceased, and the reaction mixture was stirred for an additional 16.5 h at 65 °C. After this time, the reaction was allowed to cool to room temperature and was concentrated to a volume of ca. 10 mL. A 500-mL one-necked, round-bottomed flask (note: *clearseal joint*) was charged with a solution of CH_2N_2 (ca. 18 mmol, generated from diazald (5.58 g, 26.0 mmol)) in 125 mL of diethyl ether. The yellow solution was cooled to 0 °C and stirred rapidly while the

benzene solution of the acid chloride prepared above was added *via* pipette over 1 min (the flask containing the acid chloride was rinsed with two 10-mL portions of diethyl ether). The ice bath was removed after 10 min, stirring was stopped, and the reaction mixture was allowed to warm to room temperature. After 2 h, the reaction mixture was concentrated to provide 2.18 g of a yellow oil. Column chromatography on 100 g of silica gel (compound applied adsorbed on 6 g of silica gel, elution with 20% ethyl acetate-hexanes) afforded 1.33 g (45% from 3,4-dichlorocinnamic acid) of pure 4-bromo-1-diazo-4-(3,4-dichlororphenyl)-2-butanone as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) :	7.52 (d, J = 2.0 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.25 (dd, J = 8.5, 2.0 Hz, 1H), 5.40 (dd, J = 8.1, 6.1 Hz, 1H), 5.30 (br s, 1H), and 3.18 (ABX, J_{ax} = 8.1 Hz, J_{bx} = 6.1 Hz, J_{ab} = 15.7 Hz, δ_a = 3.25, δ_b = 3.10, 2H).
^{13}C NMR (75 MHz, $CDCl_3$) :	189.3, 141.1, 132.9, 132.7, 130.8, 129.3, 126.6, 56.0, 49.6, and 45.6.
IR (CCl_4) :	3100, 2110, 1610, 1550, 1470, 1400, 1370, 1335, 1250, 1200, 1130, 1090, 1030, and 1000 cm^{-1}.
UV (CH_3CN) :	352 (ε = 1,100), 241 (17,900), 207 (29,300), and 198 (15,800) nm.
HRMS (EI) :	Calculated for $C_{10}H_7BrCl_2N_2O$: 319.9119. Found: 319.9114.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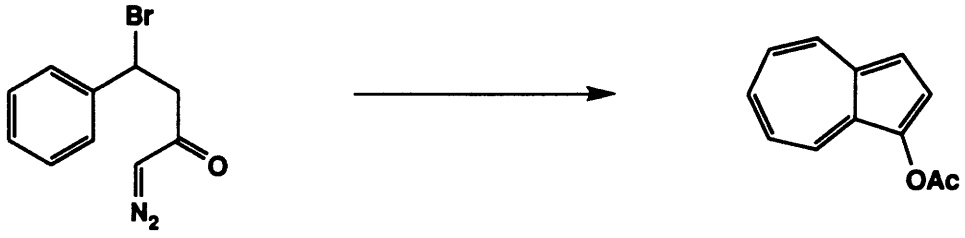
41.9



1-Acetoxyazulene (252).

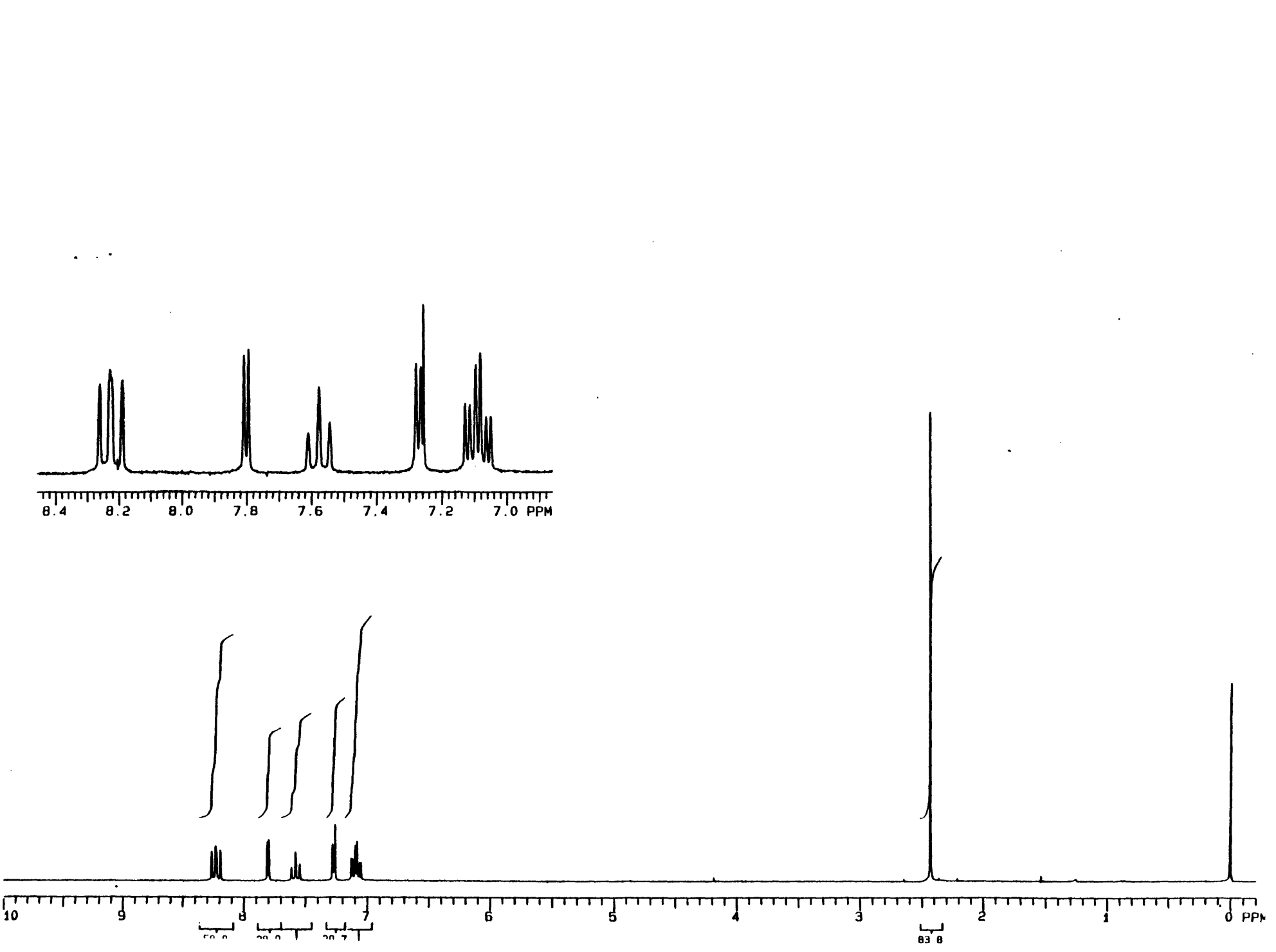
A 500-mL, three-necked, round-bottomed flask equipped with rubber septum, 125-mL pressure equalizing addition funnel, and an argon inlet adaptor was charged with rhodium pivalate (0.0220 g, 0.0395 mmol) and 120 mL of dichloromethane. The addition funnel was charged with 4-bromo-1-diazo-4-phenyl-2-butanone (2.00 g, 7.89 mmol) and 75 mL of dichloromethane. The solution of the diazo ketone was added dropwise over 1.5 h to the rapidly stirred solution of the catalyst. The addition funnel was rinsed with 5 mL of dichloromethane, and the green reaction mixture was stirred for 5 min. Acetic anhydride (4.02 g, 3.70 mL, 39.5 mmol) was added in one portion via syringe, and then 4-dimethylaminopyridine (2.89 g, 23.7 mmol) was immediately added in one portion. The resulting deep blue solution was stirred for 5 min and then treated with 10 mL of methanol. After stirring an additional 10 min, the reaction mixture was poured into a 1-L separatory funnel containing 100 mL of dichloromethane and 200 mL of an aqueous 3% HCl solution. The organic phase was separated, washed with 150 mL of aqueous 3% HCl solution and 200 mL of brine, dried over magnesium sulfate, and concentrated to provide 1.40 g of a blue oil. Column chromatography on 50 g of silica gel (elution with 5% ethyl acetate-hexanes) afforded 0.948 g (64%) of 1-acetoxyazulene as blue needles, mp 53.5-54.5 °C (lit.[62] mp 47.5-50.2 °C).

^{1}H NMR (300 MHz, $CDCl_3$) :	8.25 (d, J = 9.3 Hz, 1H), 8.21 (d, J = 10.0 Hz, 1H), 7.80 (d, J = 4.2 Hz, 1H), 7.58 (app t, J = 9.7, 10.0 Hz, 1H), 7.27 (d, J = 4.2 Hz, 1H), 7.09 (dt, J = 4.2, 10.0 Hz, 2H), and 2.43 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) :	169.2, 138.5, 138.1, 137.8, 135.5, 132.1, 127.8,

126.1, 122.6, 121.7, 113.8, and 20.9.

IR (CCl_4) : 3030, 2810, 1765, 1580, 1545, 1500, 1400, 1370, 1320, 1220, 1205, and 1030 cm^{-1}.

UV-Vis max (hexane) : 732 (ε = 101), 663 (258), 608 (292), 586 (252), 347 (2,933), 277 (30,166), 238 (8,845), and 213 (3,352) nm.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7.8
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10
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4
3
2
1
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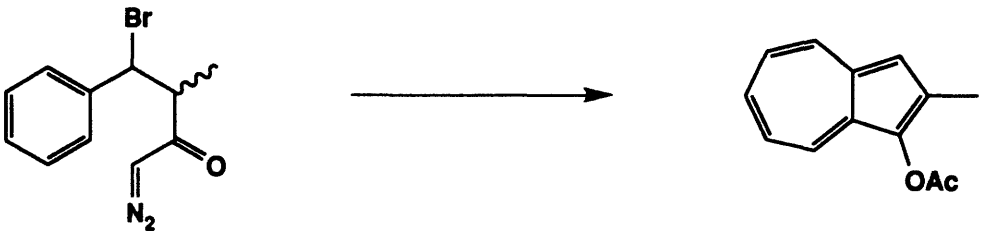
83.8

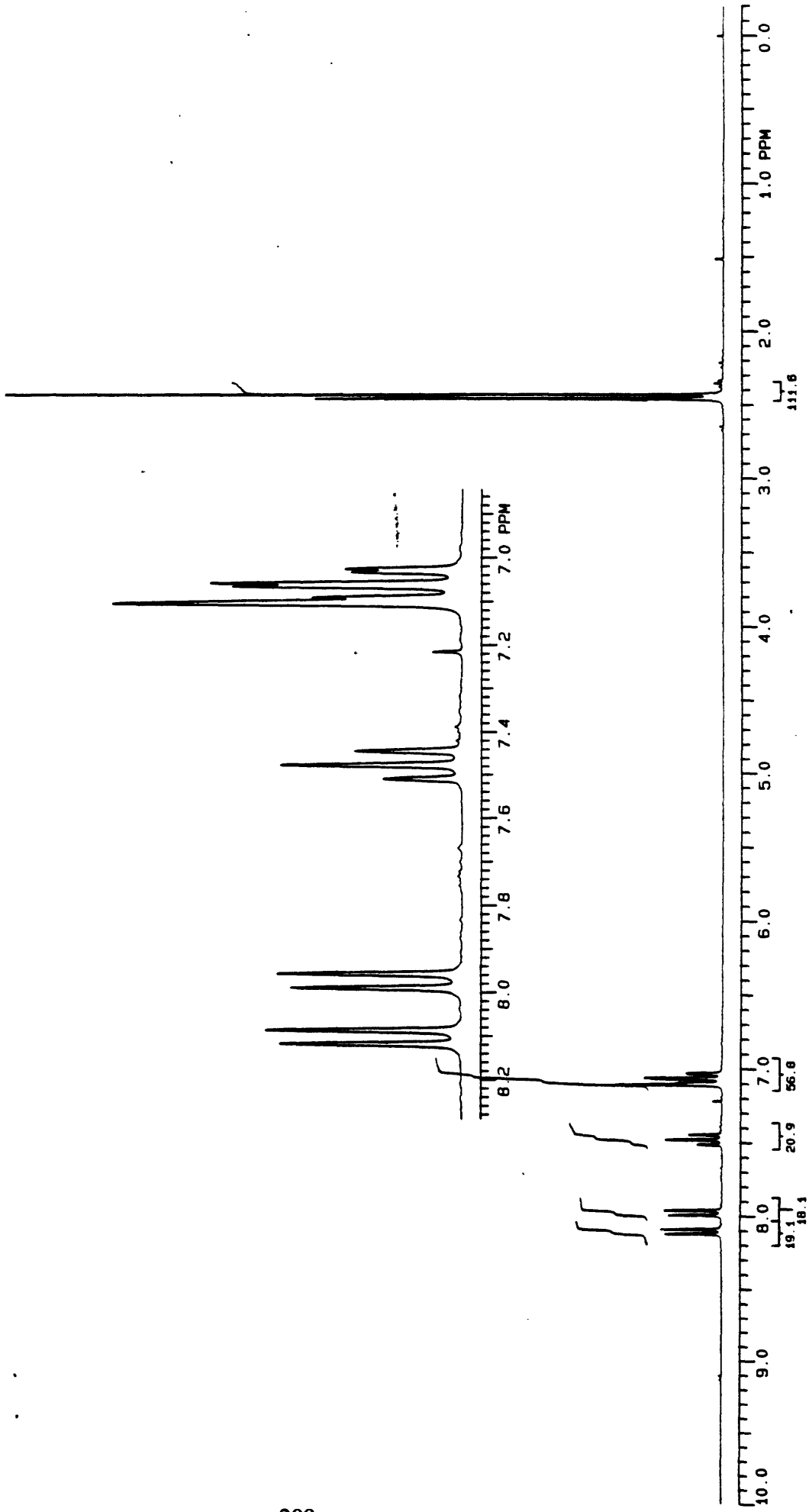


1-Acetoxy-2-methylazulene (254).

A 50-mL, three-necked, round-bottomed flask equipped with rubber septum, 15-mL pressure equalizing addition funnel, and an argon inlet adaptor was charged with rhodium pivalate (0.007 g, 0.0130 mmol) and 10 mL of dichloromethane. The addition funnel was charged with 4-bromo-1-diazo-3-methyl-4-phenyl-2-butanone (0.350 g, 1.31 mmol) and 8 mL of dichloromethane. The solution of the diazo ketone was added dropwise over 15 min to the rapidly stirred solution of the catalyst. The addition funnel was rinsed with 2 mL of dichloromethane, and the reaction mixture was stirred for 2 min. Acetic anhydride (0.669 g, 0.620 mL, 6.55 mmol) was added in one portion via syringe, and then 4-dimethylaminopyridine (0.480 g, 3.93 mmol) was immediately added in one portion. The resulting blue solution was stirred for 2 min and then treated with 2 mL of methanol. After stirring an additional 2 min, the reaction mixture was poured into a 125-mL separatory funnel containing 30 mL of dichloromethane and 30 mL of an aqueous 3% HCl solution. The organic phase was separated, washed with two 30-mL portions of aqueous 3% HCl solution and 30 mL of brine, dried over magnesium sulfate, filtered through a small pad of neutral alumina, and concentrated to provide 0.221 g of a blue oil. Column chromatography on 45 g of silica gel (elution with benzene) afforded 0.149 g (58%) of 1-acetoxy-2-methylazulene as blue needles, mp 58.5-59.5 °C.

^{1}H NMR (300 MHz, $CDCl_3$) :	8.10 (d, J = 9.4 Hz, 1H), 7.97 (d, J = 9.7 Hz, 1H), 7.48 (app t, J = 9.7, 10.1 Hz, 1H), 7.03-7.10 (m, 3H), 2.46 (s, 3H), and 2.43 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) :	169.9, 140.2, 136.7, 136.5, 135.9, 135.6, 130.1, 127.3, 123.0, 122.2, 114.5, 20.6, and 13.4.

IR (CCl_4) :	3020, 2970, 2870, 1765, 1580, 1540, 1500, 1400, 1370, 1350, 1290, 1200, 1110, 1000, and 905 cm^{-1}.	
UV-Vis max (CH_3CN) :	684 (ε = 120), 641 (270), 621 (270), 585 (310), 573 (280), 550 (250), 346 (4,270), 283 (49,840), 279 (47,465), and 274 (45,570) nm.	
Elemental Analysis :	Calculated for $C_{13}H_{12}O_2$:	C, 77.98; H, 6.04.
	Found :	C, 77.73; H, 5.66.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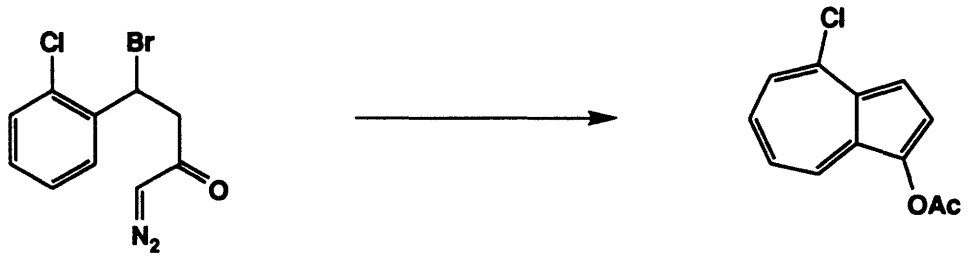
56.8
20.9
19.1
18.1

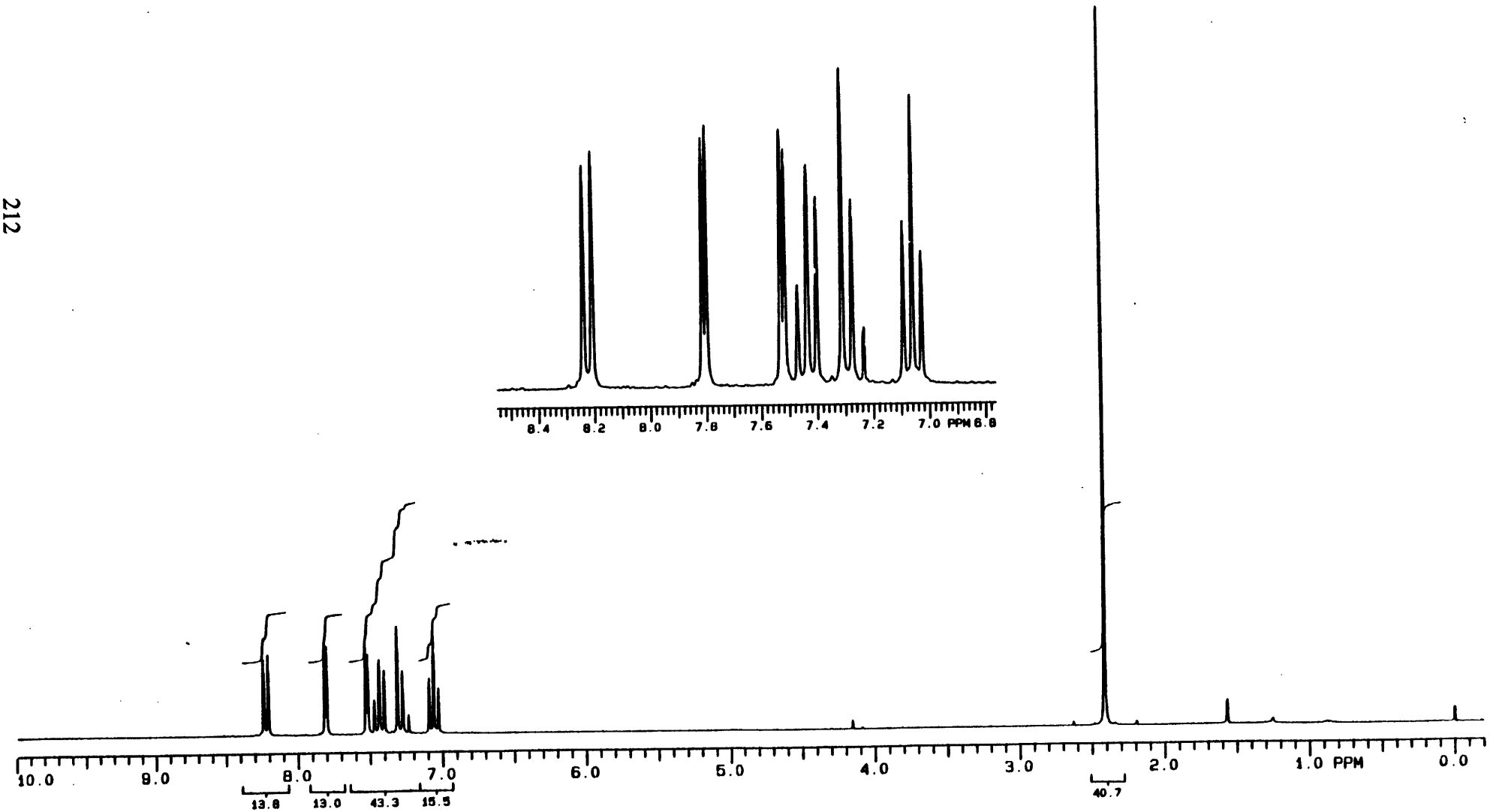


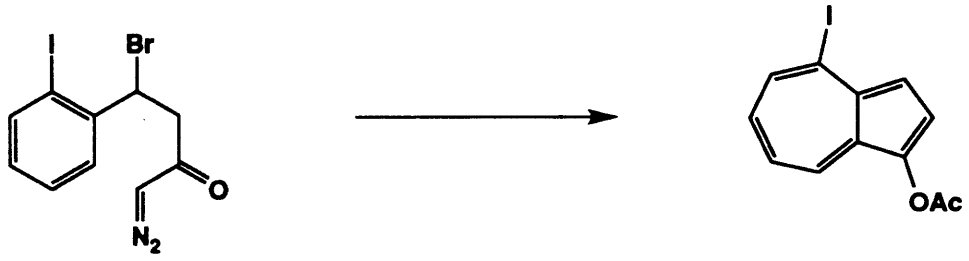
1-Acetoxy-4-chloroazulene (255).

A 50-mL, three-necked, round-bottomed flask equipped with rubber septum, 15-mL pressure equalizing addition funnel, and an argon inlet adaptor was charged with rhodium pivalate (0.007 g, 0.0122 mmol) and 10 mL of dichloromethane. The addition funnel was charged with 4-bromo-4-(2-chlorophenyl)-1-diazo-2-butanone (0.350 g, 1.22 mmol) and 8 mL of dichloromethane. The solution of the diazo ketone was added dropwise over 15 min to the rapidly stirred solution of the catalyst. The addition funnel was rinsed with 2 mL of dichloromethane, and the reaction mixture was stirred for 2 min. Acetic anhydride (0.621 g, 0.575 mL, 6.09 mmol) was added in one portion via syringe, and then 4-dimethylaminopyridine (0.446 g, 3.65 mmol) was immediately added in one portion. The resulting blue solution was stirred for 2 min and then treated with 2 mL of methanol. After stirring an additional 2 min, the reaction mixture was poured into a 125-mL separatory funnel containing 30 mL of dichloromethane and 30 mL of an aqueous 3% HCl solution. The organic phase was separated, washed with two 30-mL portions of aqueous 3% HCl solution and 30 mL of brine, dried over magnesium sulfate, filtered through a small pad of neutral alumina, and concentrated to provide 0.214 g of a blue oil. Column chromatography on 15 g of silica gel (elution with 5% ethyl acetate-hexanes) afforded 0.157 g (58%) of 1-acetoxy-4-chloroazulene as a blue-gray solid, mp 55.5-56.5 °C.

^{1}H NMR (300 MHz, $CDCl_3$) : 8.22 (d, J = 9.7 Hz, 1H), 7.80 (d, J = 4.2 Hz, 1H), 7.52 (d, J = 4.2 Hz, 1H), 7.44 (app t, J = 9.5, 10.8 Hz, 1H), 7.29 (d, J = 10.8 Hz, 1H), 7.06 (app t, J = 9.5, 9.7 Hz, 1H), and 2.41 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) :	169.1, 144.0, 139.4, 136.0, 132.4, 130.1, 128.0, 126.3, 124.5, 121.1, 114.3, and 21.0.	
IR (CCl_4) :	3020, 1760, 1585, 1550, 1495, 1450, 1395, 1365, 1310, 1230, 1200, 1060, 1030, 990, 925, 910, and 865 cm^{-1}.	
UV-Vis max (hexane) :	657 (ε = 267), 605 (311), 520 (114), 351 (4,130), 337 (2,970), 284 (35,440), 245 (23,670), and 219 (8,960) nm.	
Elemental Analysis :	Calculated for $C_{12}H_9ClO_2$:	C, 65.32; H, 4.11.
	Found :	C, 65.31; H, 3.99.


8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0 PPM 6.8
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0 PPM
0.0
13.8
13.0
43.3
15.5
40.7

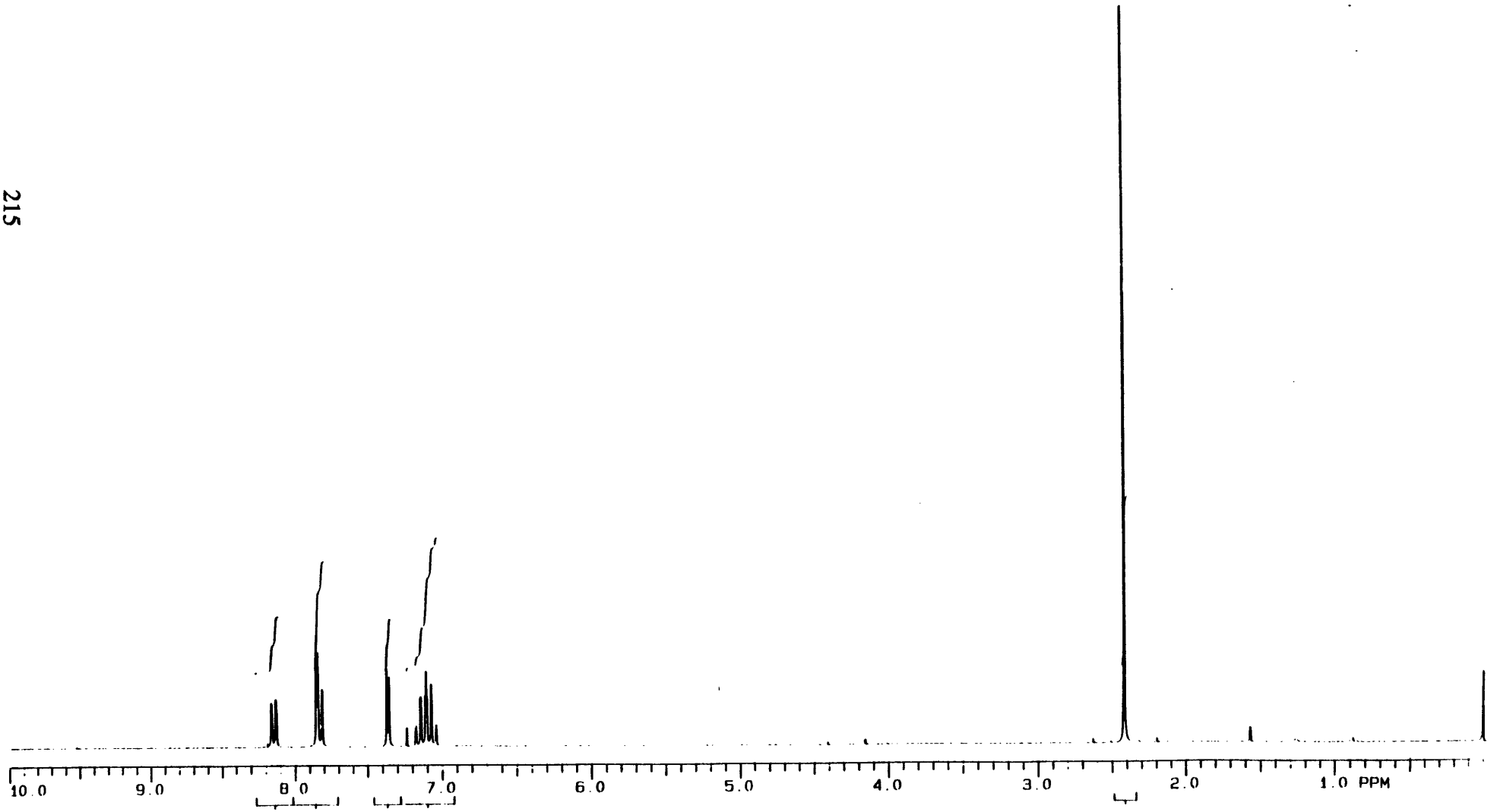


1-Acetoxy-4-iodoazulene (256).

A 250-mL, three-necked, round-bottomed flask equipped with rubber septum, 60-mL pressure equalizing addition funnel, and an argon inlet adaptor was charged with rhodium pivalate (0.018 g, 0.0325 mmol) and 55 mL of dichloromethane. The addition funnel was charged with 4-bromo-4-(2-iodophenyl)-1-diazo-2-butanone (1.23 g, 3.25 mmol) and 30 mL of dichloromethane. The solution of the diazo ketone was added dropwise over 60 min to the rapidly stirred solution of the catalyst. The addition funnel was rinsed with 5 mL of dichloromethane, and the reaction mixture was stirred for 5 min. Acetic anhydride (1.66 g, 1.50 mL, 16.2 mmol) was added in one portion via syringe, and then 4-dimethylaminopyridine (1.19 g, 9.74 mmol) was immediately added in one portion. The resulting blue solution was stirred for 5 min and then treated with 2 mL of methanol. After stirring an additional 5 min, the reaction mixture was poured into a 500-mL separatory funnel containing 50 mL of dichloromethane and 100 mL of an aqueous 5% HCl solution. The organic phase was separated, washed with 30 mL of aqueous 5% HCl solution and 100 mL of brine, dried over magnesium sulfate, filtered, and concentrated to provide 1.03 g of a blue oil. Column chromatography on 50 g of silica gel (elution with 5% ethyl acetate-hexanes) afforded 0.687 g (68%) of 1-acetoxy-4-iodoazulene as a metallic blue solid. An analytical sample was prepared by recrystallization from hexanes (-20 °C), mp 76.0-77.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) : 8.14 (d, J = 10.0 Hz, 1H), 7.81-7.85 (m, 2H), 7.36 (d, J = 4.5 Hz, 1H), 7.07-7.14 (m, 2H), and 2.41 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) :	168.9, 140.2, 136.3, 134.7, 131.9, 128.9, 125.4, 122.7, 121.7, 116.9, 103.9, and 21.0.	
IR (CCl_4) :	2950, 2920, 1755, 1545, 1490, 1395, 1365, 1310, 1200, 1030, and 980 cm^{-1}.	
UV-Vis max (hexane) :	611 (ε = 380), 352 (7,075), 316 (15,710), 296 (53,475), 279 (47,230), 261 (61,175), 231 (15,810), and 192 (22,260) nm.	
Elemental Analysis :	Calculated for $C_{12}H_9IO_2$:	C, 46.18; H, 2.91.
	Found :	C, 46.08; H, 2.83.

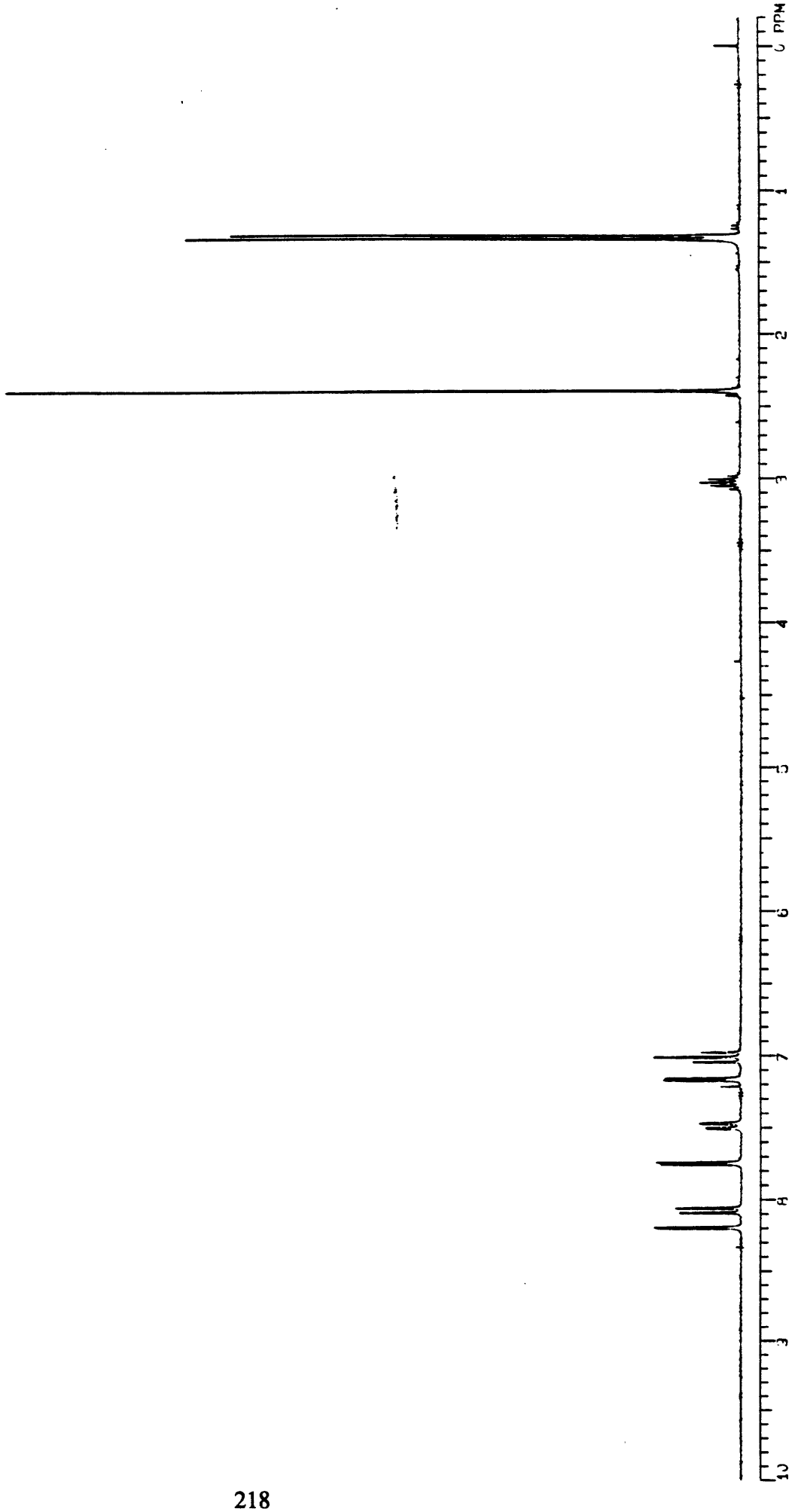

10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0 PPM

1-Acetoxy-5-isopropylazulene (257).

A 50-mL, three-necked, round-bottomed flask equipped with rubber septum, 15-mL pressure equalizing addition funnel, and an argon inlet adaptor was charged with rhodium pivalate (0.007 g, 0.0120 mmol) and 10 mL of diethyl ether. The addition funnel was charged with 4-bromo-1-diazo-4-(3-isopropylphenyl)-2-butanone (0.355 g, 1.20 mmol) and 8 mL of diethyl ether. The solution of the diazo ketone was added dropwise over 15 min to the rapidly stirred solution of the catalyst. The addition funnel was rinsed with 2 mL of diethyl ether, and the green reaction mixture was stirred for ca. 2 min. Acetic anhydride (0.614 g, 0.56 mL, 6.01 mmol) was added in one portion via syringe, and then 4-dimethylaminopyridine (0.441 g, 3.61 mmol) in 2 mL of dichloromethane was immediately added in one portion. The resulting purple solution was stirred for 10 min and then treated with 2 mL of methanol. After stirring an additional 2 min, the reaction mixture was poured into a 125-mL separatory funnel containing 30 mL of diethyl ether and 30 mL of an aqueous 3% HCl solution. The organic phase was separated, washed with two 30-mL portions of aqueous 3% HCl solution and 30 mL of brine, dried over magnesium sulfate, filtered through a small pad of neutral alumina, and concentrated to provide 0.318 g of a blue oil. Column chromatography on 15 g of silica gel (elution with 5% ethyl acetate-hexanes) afforded 0.151 g (54%) of 1-acetoxy-5-isopropylazulene as a blue oil.

^{1}H NMR (300 MHz, $CDCl_3$) : 8.20 (d, J = 1.8 Hz, 1H), 8.08 (d, J = 10.0 Hz, 1H), 7.75 (d, J = 4.3 Hz, 1H), 7.49 (d, J = 9.5 Hz, 1H), 7.17 (d, J = 4.3 Hz, 1H), 7.01 (app t, J = 9.5, 10.0 Hz, 1H), 3.03 (sept, J = 6.9 Hz, 1H), 2.40 (s, 3H), and 1.33 (d, J = 6.9 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) :	169.4, 142.7, 138.1, 137.0, 135.7, 130.6, 127.9, 125.6, 121.6, 121.5, 112.9, 38.4, 24.4, and 21.0.	
IR (thin film) :	2960, 2920, 2860, 1755, 1580, 1495, 1460, 1395, 1365, 1305, 1205, 1030, 920, and 755 cm^{-1}.	
UV-Vis max (hexane) :	614 (ε = 119), 352 (2,170), 279 (21,570), and 225 (67,000) nm.	
Elemental Analysis :	Calculated for $C_{15}H_{16}O_2$:	C, 78.92; H, 7.06.
	Found :	C, 79.14; H, 6.87.


0 PPM
1
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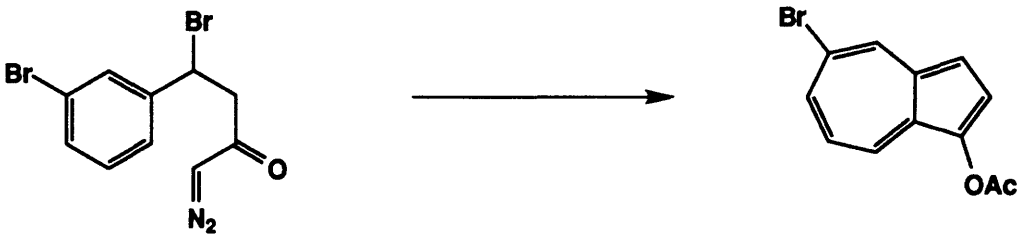
10

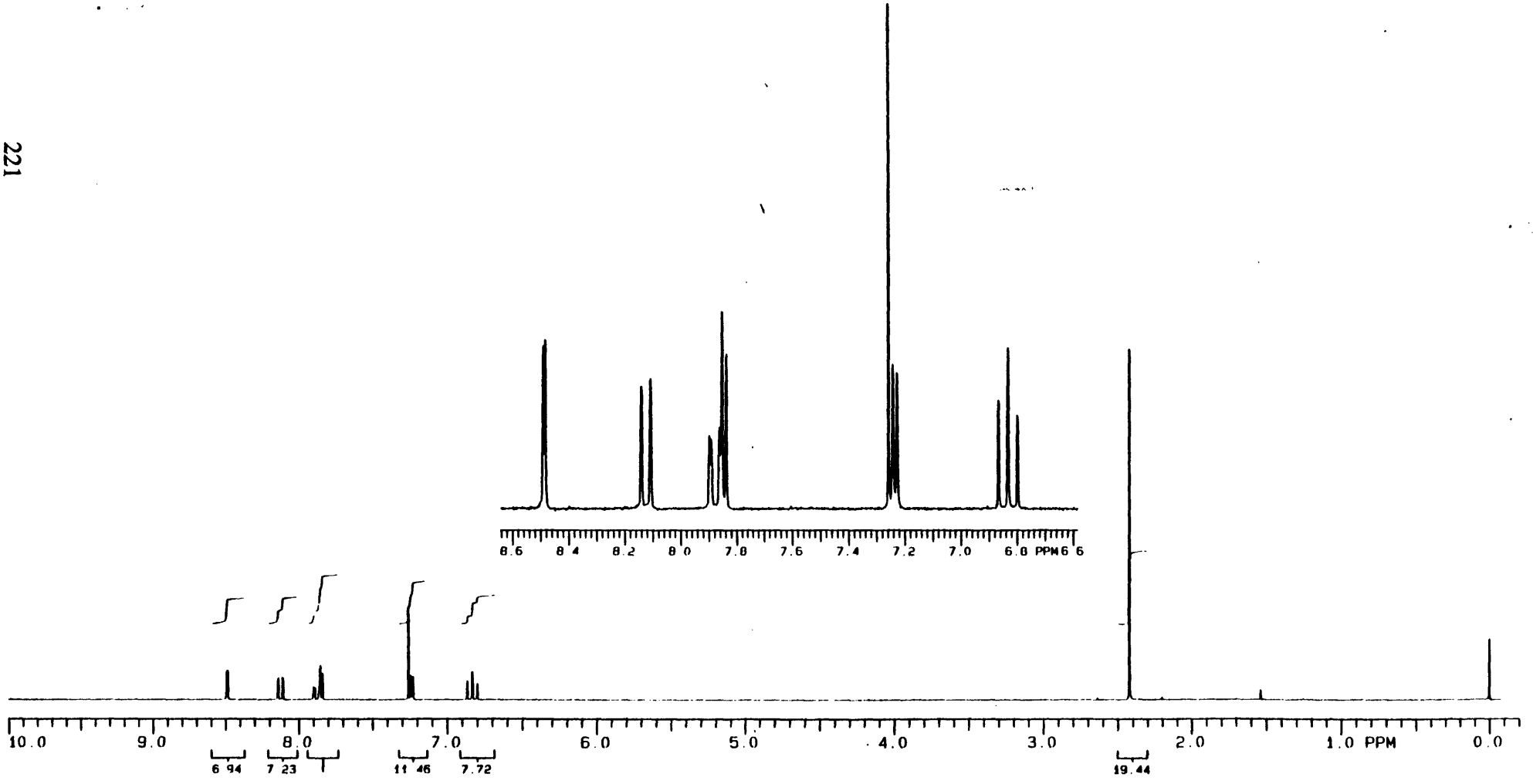


1-Acetoxy-5-bromoazulene (258).

A 50-mL, three-necked, round-bottomed flask equipped with rubber septum, 15-mL pressure equalizing addition funnel, and an argon inlet adaptor was charged with rhodium pivalate (0.006 g, 0.0105 mmol) and 10 mL of dichloromethane. The addition funnel was charged with 4-bromo-4-(3-bromophenyl)-1-diazo-2-butanone (0.350 g, 1.05 mmol) and 8 mL of dichloromethane. The solution of the diazo ketone was added dropwise over 12 min to the rapidly stirred solution of the catalyst. The addition funnel was rinsed with 2 mL of dichloromethane, and the reaction mixture was stirred for 2 min. Acetic anhydride (0.538 g, 0.500 mL, 5.27 mmol) was added in one portion via syringe, and then 4-dimethylaminopyridine (0.386 g, 3.16 mmol) was immediately added in one portion. The resulting blue-black solution was stirred for 2 min and then treated with 2 mL of methanol. After stirring an additional 2 min, the reaction mixture was poured into a 125-mL separatory funnel containing 30 mL of dichloromethane and 30 mL of an aqueous 3% HCl solution. The organic phase was separated, washed with two 30-mL portions of aqueous 3% HCl solution and 50 mL of brine, dried over magnesium sulfate, filtered through a small pad of neutral alumina, and concentrated to provide 0.198 g of a blue oil. Column chromatography on 15 g of silica gel (elution with 5% ethyl acetate-hexanes) afforded 0.109 g (39%) of 1-acetoxy-5-bromoazulene as an olive green solid, mp 60.5-61.5 °C.

^{1}H NMR (300 MHz, $CDCl_3$) : 8.49 (d, J = 2.1 Hz, 1H), 8.13 (d, J = 9.8 Hz, 1H), 7.90-7.84 (m, 2H), 7.24 (d, J = 4.3 Hz, 1H), 6.83 (app t, J = 9.8, 10.0 Hz, 1H), and 2.42 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) :	168.9, 141.0, 140.9, 138.6, 133.6, 131.3, 129.9, 126.2, 120.7, 117.4, 114.7, and 21.0.	
IR (CCl_4) :	2900, 1765, 1580, 1545, 1420, 1395, 1365, 1300, 1200, 1030, 995, and 895 cm^{-1}.	
UV-Vis max (hexane) :	690 (ε = 273), 632 (302), 601 (250), 371 (3,230), 362 (2,440), 351 (3,980), 347 (2,860), 337 (2,070), and 278 (28,900) nm.	
Elemental Analysis :	Calculated for $C_{12}H_9BrO_2$:	C, 54.37; H, 3.42.
	Found :	C, 54.59; H, 3.29.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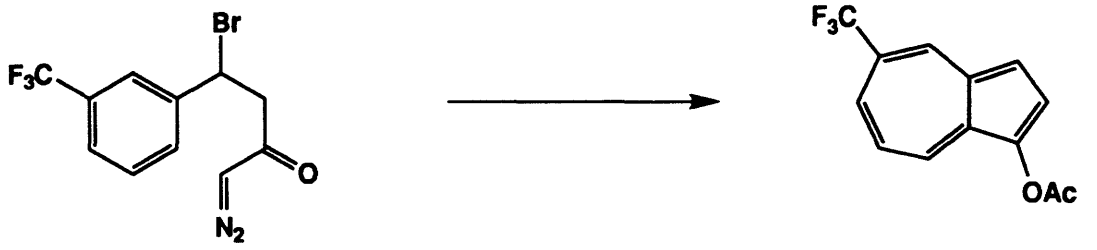
10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 PPM 0.0
6.94 7.23 11.46 7.72 19.44

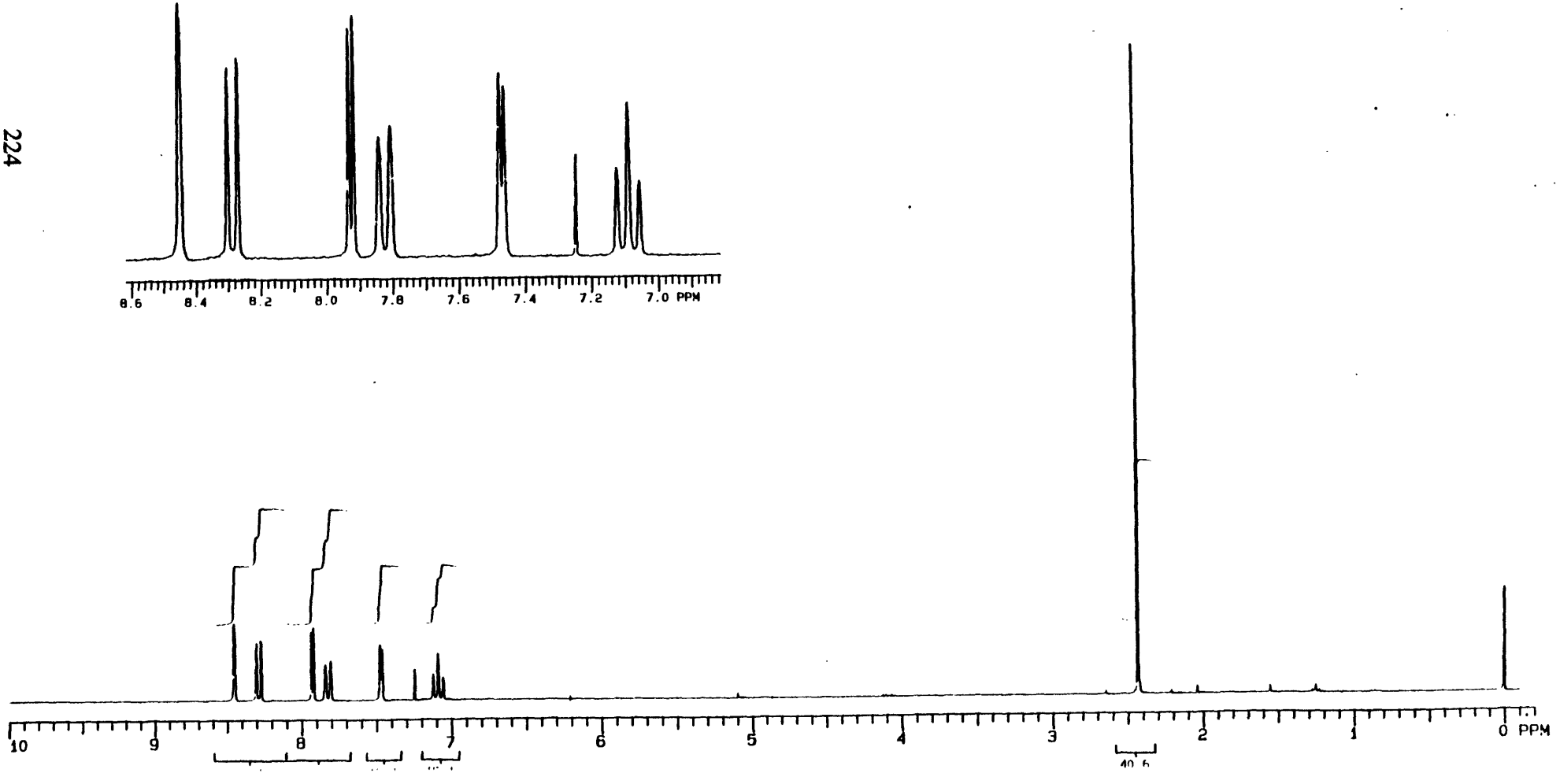


1-Acetoxy-5-(trifluoromethyl)azulene (259).

A 50-mL, three-necked, round-bottomed flask equipped with rubber septum, 15-mL pressure equalizing addition funnel, and an argon inlet adaptor was charged with rhodium pivalate (0.006 g, 0.0105 mmol) and 10 mL of dichloromethane. The addition funnel was charged with 4-bromo-4-((3-trifluoromethyl)phenyl)-1-diazo-2-butanone (0.343 g, 1.07 mmol) and 8 mL of dichloromethane. The solution of the diazo ketone was added dropwise over 13 min to the rapidly stirred solution of the catalyst. The addition funnel was rinsed with 2 mL of dichloromethane, and the reaction mixture was stirred for 2 min. Acetic anhydride (0.538 g, 0.500 mL, 5.27 mmol) was added in one portion via syringe, and then 4-dimethylaminopyridine (0.386 g, 3.16 mmol) was immediately added in one portion. The resulting brown solution was stirred for 2 min and then treated with 2 mL of methanol. After stirring an additional 2 min, the reaction mixture was poured into a 125-mL separatory funnel containing 30 mL of dichloromethane and 30 mL of an aqueous 3% HCl solution. The organic phase was separated, washed with two 30-mL portions of aqueous 3% HCl solution and 30 mL of brine, dried over magnesium sulfate, filtered through a small pad of neutral alumina, and concentrated to provide 0.187 g of a blue-green oil. Column chromatography on 15 g of silica gel (elution with 5% ethyl acetate-hexanes) afforded 0.109 g (40%) of 1-acetoxy-5-(trifluoromethyl)azulene as a blue solid, mp 43.5-44.5 °C.

^{1}H NMR (300 MHz, $CDCl_3$) : 8.45 (d, J = 1.4 Hz, 1H), 8.29 (d, J = 9.5 Hz, 1H), 7.92 (d, J = 4.3 Hz, 1H), 7.83 (d, J = 4.3 Hz, 1H), 7.47 (d, J = 4.3 Hz, 1H), 7.09 (app t, J = 9.5, 10.4, 1H), and 2.43 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) :	168.8, 140.5, 134.8, 134.7, 134.4, 134.1, 134.0, 133.3, 129.4, 126.2, 120.5, 118.6, and 21.0.	
IR (CCl_4) :	2920, 2840, 1770, 1580, 1500, 1460, 1400, 1370, 1330, 1290, 1260, 1200, 1170, 1130, 1055, 1035, 1000, and 915 cm^{-1}.	
UV-Vis max (hexane) :	608 (ε = 255), 583 (221), 352 (8,474), 278 (61,858), and 215 (11,863) nm.	
Elemental Analysis :	Calculated for $C_{13}H_9F_3O_2$:	C, 61.42; H, 3.56.
	Found :	C, 61.43; H, 3.63.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8.4
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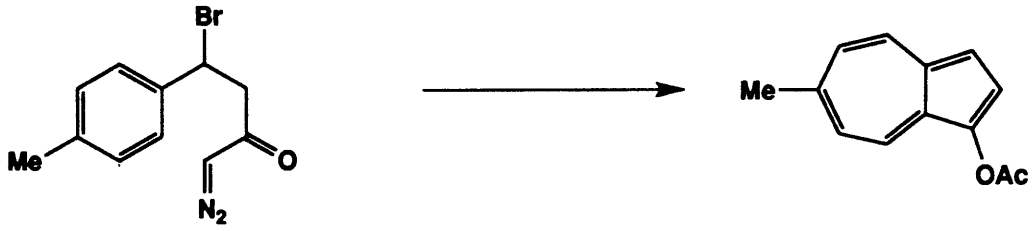
8.0
7.8
7.6
7.4
7.2
7.0 PPM
10
9
8
7
6
5
4
3
2
1
0 PPM
40.6

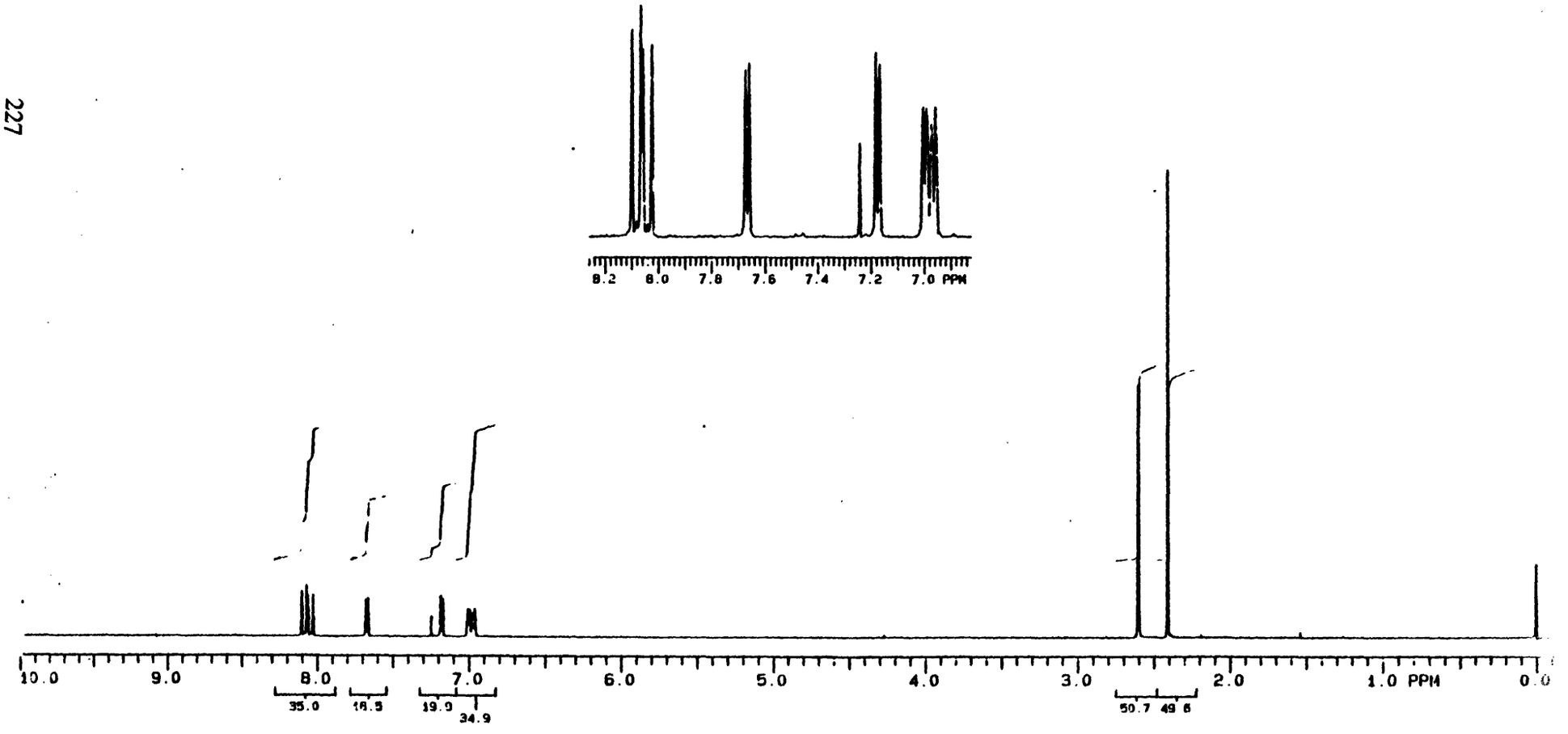


1-Acetoxy-6-methylazulene (260).

A 50-mL, three-necked, round-bottomed flask equipped with rubber septum, 15-mL pressure equalizing addition funnel, and an argon inlet adaptor was charged with rhodium pivalate (0.004 g, 0.0090 mmol) and 8 mL of dichloromethane. The addition funnel was charged with 4-bromo-4-(4-methylphenyl)-1-diazo-2-butanone (0.216 g, 0.809 mmol) and 5 mL of dichloromethane. The solution of the diazo ketone was added dropwise over 15 min to the rapidly stirred solution of the catalyst. The addition funnel was rinsed with 2 mL of dichloromethane, and the reaction mixture was stirred for 2 min. Acetic anhydride (0.413 g, 0.381 mL, 4.04 mmol) was added in one portion via syringe, and then 4-dimethylaminopyridine (0.296 g, 2.43 mmol) was immediately added in one portion. The resulting blue solution was stirred for 2 min and then treated with 2 mL of methanol. After stirring an additional 2 min, the reaction mixture was poured into a 125-mL separatory funnel containing 30 mL of dichloromethane and 30 mL of an aqueous 3% HCl solution. The organic phase was separated, washed with two 30-mL portions of aqueous 3% HCl solution and 30 mL of brine, dried over magnesium sulfate, filtered through a small pad of neutral alumina, and concentrated to provide 0.198 g of a blue oil. Column chromatography on 20 g of silica gel (elution with 5% ethyl acetate-hexanes) afforded 0.076 g (21% from 4-methylcinnamic acid) of 1-acetoxy-6-methylazulene as a blue solid, mp 67.0-67.5 °C.

^{1}H NMR (300 MHz, $CDCl_3$) : 8.08 (d, J= 9.4 Hz, 1H), 8.04 (d, J = 10.2 Hz, 1H), 7.67 (d, J = 4.3 Hz, 1H), 7.21 (d, J = 4.3 Hz, 1H), 6.99 (d, J = 9.4 Hz, 1H), 6.98 (d J = 10.2 Hz, 1H), 2.60 (s, 3H), and 2.41 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) :	169.4, 150.5, 138.1, 137.3, 134.1, 131.1, 126.4, 125.0, 123.9, 123.6, 114.0, 28.3, and 21.1.	
IR (CCl_4) :	3030, 2920, 2880, 1765, 1580, 1495, 1430, 1400, 1370, 1315, 1210, and 1030 cm^{-1}.	
UV-Vis max (CH_3CN) :	714 (ε = 105), 645 (270), 596 (300), 368 (3,000), 352 (5,700), 349 (5,890), 335 (4,390), 281 (72,290), and 234 (18,120) nm.	
Elemental Analysis :	Calculated for $C_{13}H_{12}O_2$:	C, 77.98; H, 6.04.
	Found :	C, 77.84; H, 6.04.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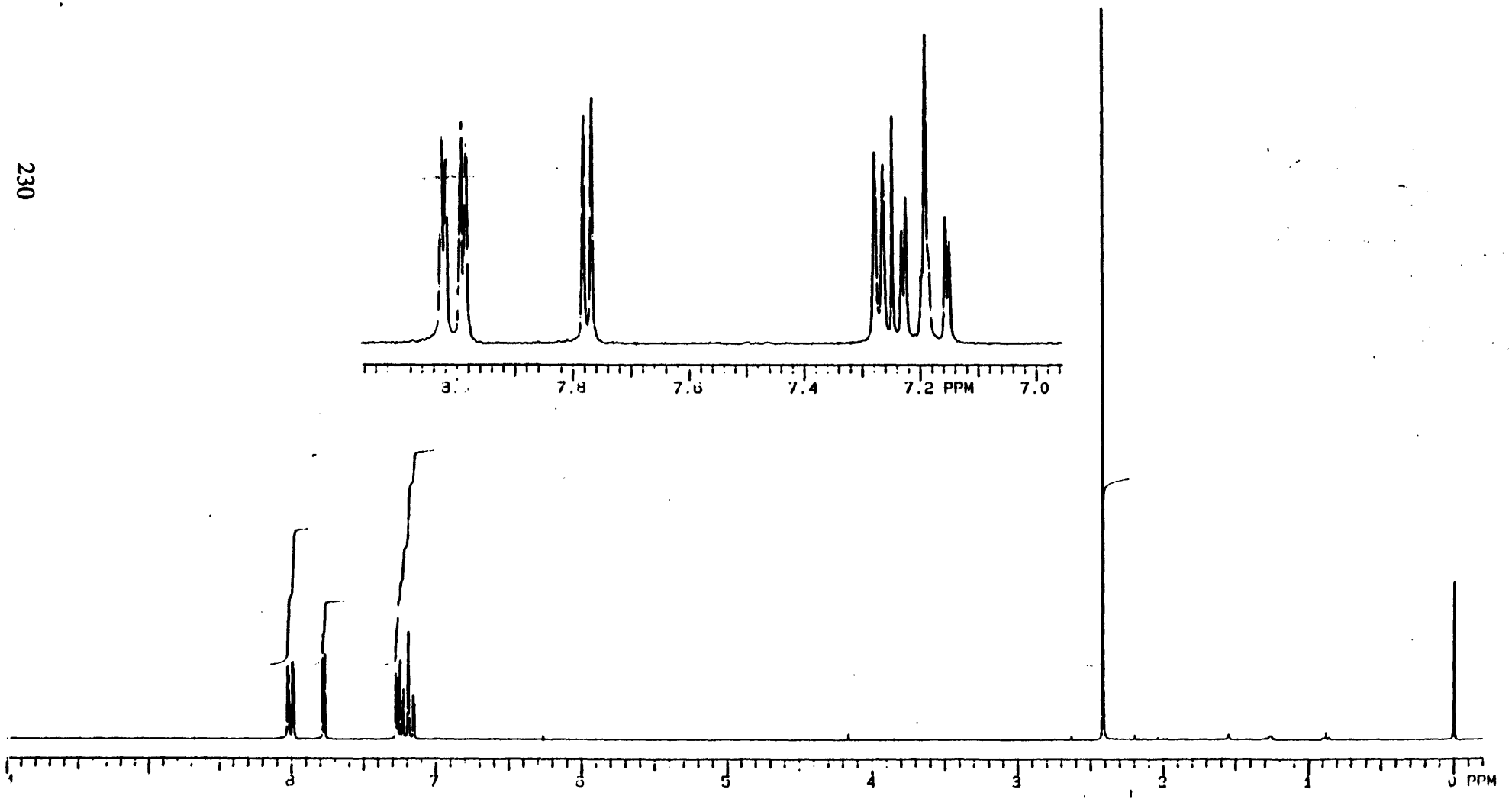
7.6
7.4
7.2
7.0 PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0 PPM
0.0
35.0
16.5
19.9
34.9
50.7
49.6

1-Acetoxy-6-chloroazulene (261).

A 250-mL, three-necked, round-bottomed flask equipped with rubber septum, 60-mL pressure equalizing addition funnel, and an argon inlet adaptor was charged with rhodium pivalate (0.0120 g, 0.0210 mmol) and 40 mL of dichloromethane. The addition funnel was charged with 4-bromo-4-(4-chlorophenyl)-1-diazo-2-butanone (1.21 g, 4.21 mmol) and 35 mL of dichloromethane. The solution of the diazo ketone was added dropwise over 30 min to the rapidly stirred solution of the catalyst. The addition funnel was rinsed with 5 mL of dichloromethane, and the green reaction mixture was stirred for 3 min. Acetic anhydride (2.15 g, 2.00 mL, 21.0 mmol) was added in one portion via syringe, and then 4-dimethylaminopyridine (1.54 g, 12.6 mmol) was immediately added in one portion. The resulting deep blue solution was stirred for 2 min and then treated with 5 mL of methanol. After stirring an additional 2 min, the reaction mixture was poured into a 500-mL separatory funnel containing 100 mL of dichloromethane and 100 mL of an aqueous 3% HCl solution. The organic phase was separated, washed with two 100-mL portions of aqueous 3% HCl solution and 100 mL of brine, dried over magnesium sulfate, filtered through a small pad of neutral alumina, and concentrated to provide 0.724 g of a blue solid. Column chromatography on 50 g of silica gel (elution with 5% ethyl acetate-hexanes) afforded 0.569 g (61%) of 1-acetoxy-6-chloroazulene as metallic blue flakes, mp 66.5-67.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) : 8.01 (d, J = 10.2 Hz, 1H), 8.00 (d, J = 10.6 Hz, 1H), 7.77 (d, J = 4.3 Hz, 1H), 7.27 (d, J = 4.3 Hz, 1H), 7.23-7.16 (m, 2H), and 2.42 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) :	169.0, 145.6, 139.6, 135.8, 133.9, 130.3, 128.0, 124.7, 122.8, 122.3, 116.1, and 21.0.	
IR (CCl_4) :	2880, 1750, 1565, 1510, 1465, 1375, 1345, 1290, 1230, 1185, 1010, and 980 cm^{-1}.	
UV-Vis max (hexane) :	777 (ε = 100), 664 (252), 606 (290), 582 (250), 561 (212), 304 (6,730), 283 (61,500), 237 (9,270), and 217 (10,205) nm.	
Elemental Analysis :	Calculated for $C_{12}H_9ClO_2$:	C, 65.32; H, 4.11; Cl, 16.07.
	Found :	C, 65.16; H, 4.17; Cl, 15.88.


7.8
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7.0
8
7
6
5
4
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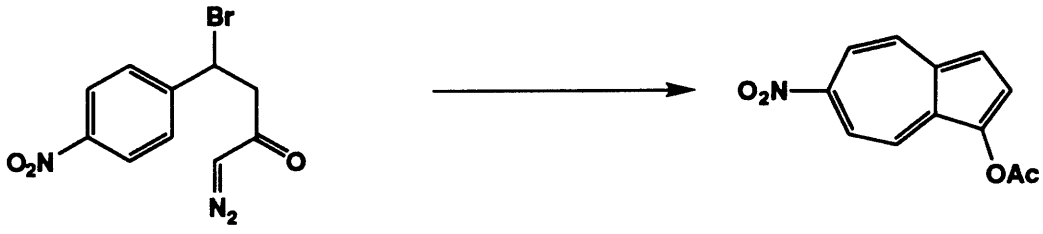
2
1
0 PPM

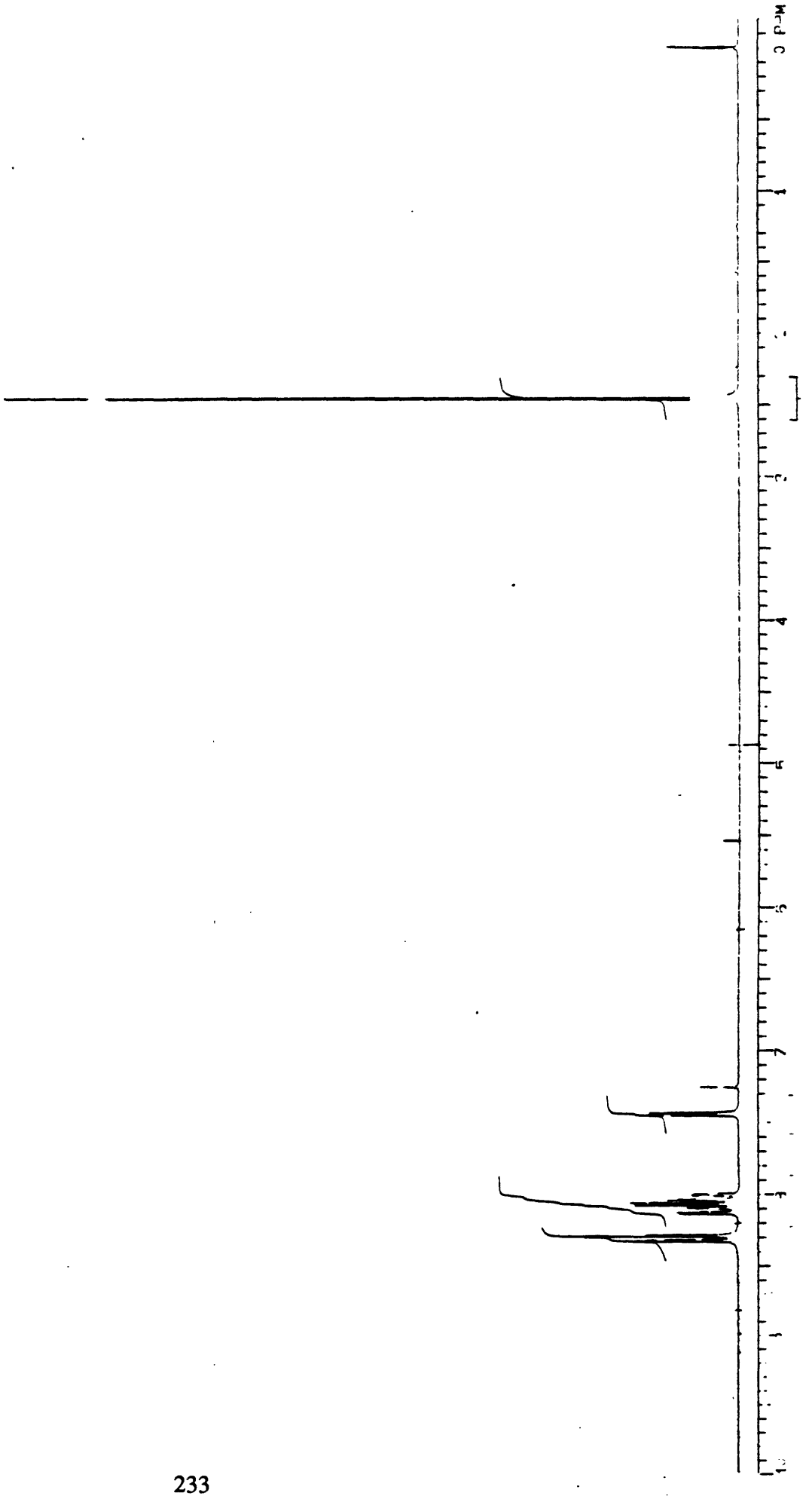


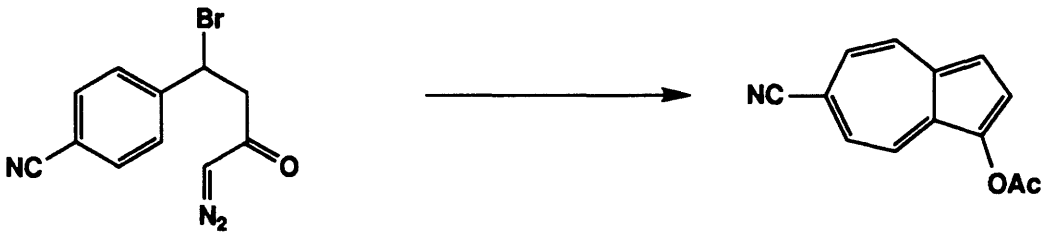
1-Acetoxy-6-nitroazulene (262).

A 50-mL, three-necked, round-bottomed flask equipped with rubber septum, 15-mL pressure equalizing addition funnel, and an argon inlet adaptor was charged with rhodium pivalate (0.007 g, 0.0130 mmol) and 10 mL of dichloromethane. The addition funnel was charged with 4-bromo-4-(4-nitrophenyl)-1-diazo-2-butanone (0.393 g, 1.32 mmol) and 8 mL of dichloromethane. The solution of the diazo ketone was added dropwise over 15 min to the rapidly stirred solution of the catalyst. The addition funnel was rinsed with 2 mL of dichloromethane, and the reaction mixture was stirred for 2 min. Acetic anhydride (0.673 g, 0.622 mL, 6.60 mmol) was added in one portion via syringe, and then 4-dimethylaminopyridine (0.483 g, 3.96 mmol) was immediately added in one portion. The resulting brown solution was stirred for 2 min and then treated with 2 mL of methanol. After stirring an additional 2 min, the reaction mixture was poured into a 125-mL separatory funnel containing 30 mL of dichloromethane and 30 mL of an aqueous 3% HCl solution. The organic phase was separated, washed with two 30-mL portions of aqueous 3% HCl solution and 30 mL of brine, dried over magnesium sulfate, filtered through a small pad of neutral alumina, and concentrated to provide 0.124 g of a green oil. Column chromatography on 20 g of silica gel (elution with 20% ethyl acetate-hexanes) afforded 0.065 g (21%) of 1-acetoxy-6-nitroazulene as a brown solid, mp 97.0-97.5 °C.

^{1}H NMR (300 MHz, $CDCl_3$) :	8.29-8.33 (m, 2H), 8.00-8.14 (m, 3H), 7.44 (d, J = 4.3 Hz, 1H), and 2.46 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) :	168.5, 154.0, 140.2, 136.8, 134.7, 132.8, 129.8, 126.2, 117.1, 116.3, 114.6, and 21.0.

IR (CCl_4) :	2920, 1770, 1535, 1440, 1395, 1330, 1315, 1245, 1205, 1195, 1035, 1005, and 980 cm^{-1}.	
UV-Vis max (CH_3CN) :	686 (ε = 310), 352 (565), 291 (51,500), 246 (19,850), 221 (16,700), 205 (16,300), 198 (26,900), and 193 (29,300) nm.	
Elemental Analysis :	Calculated for $C_{12}H_9NO_4$:	C, 62.34; H, 3.92; N, 6.06.
	Found :	C, 62.39; H, 3.83; N, 5.74.



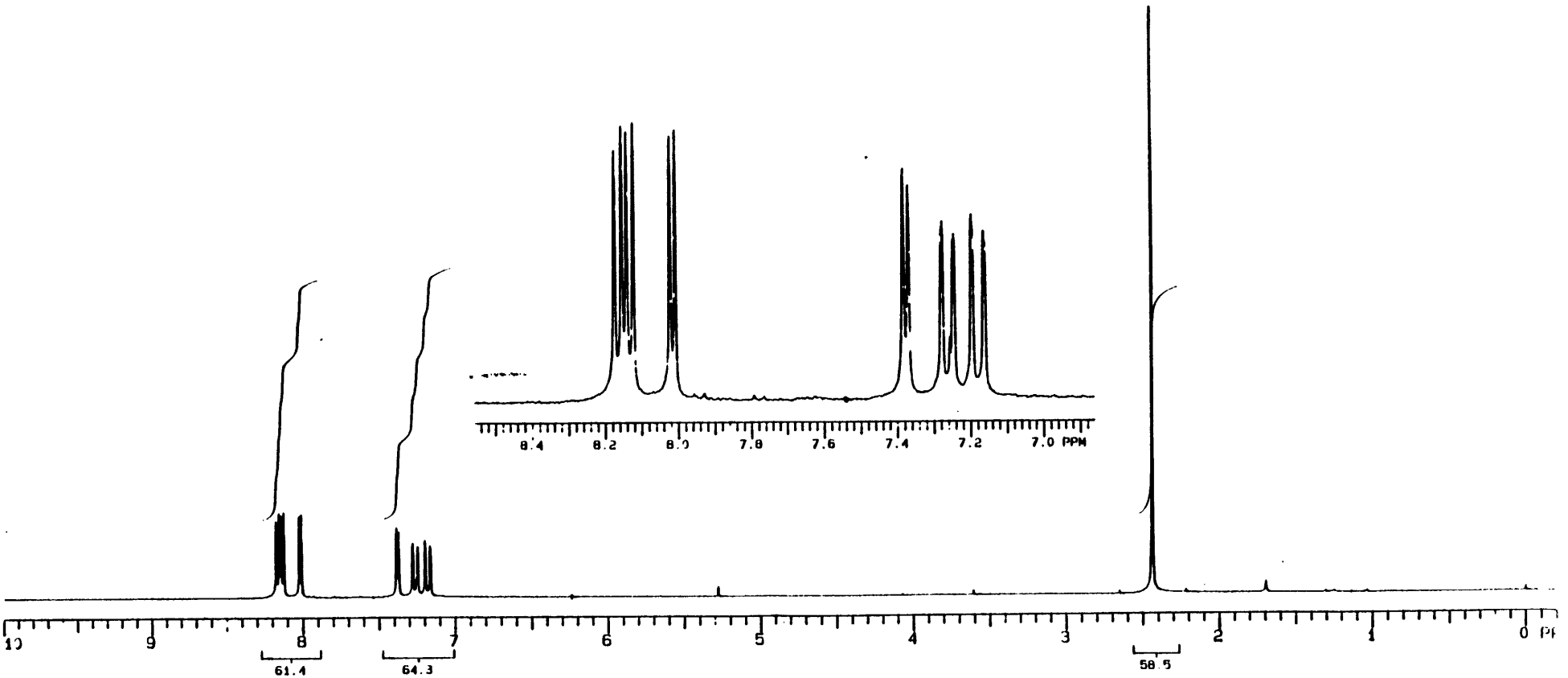


1-Acetoxy-6-cyanoazulene (263).

A 50-mL, three-necked, round-bottomed flask equipped with rubber septum, 15-mL pressure equalizing addition funnel, and an argon inlet adaptor was charged with rhodium pivalate (0.008 g, 0.0136 mmol) and 10 mL of dichloromethane. The addition funnel was charged with 4-bromo-4-(4-cyanophenyl)-1-diazo-2-butanone (0.377 g, 1.36 mmol) and 8 mL of dichloromethane. The solution of the diazo ketone was added dropwise over 14 min to the rapidly stirred solution of the catalyst. The addition funnel was rinsed with 2 mL of dichloromethane, and the reaction mixture was stirred for 2 min. Acetic anhydride (0.692 g, 0.640 mL, 6.78 mmol) was added in one portion via syringe, and then 4-dimethylaminopyridine (0.497 g, 4.07 mmol) was immediately added in one portion. The resulting green-black solution was stirred for 2 min and then treated with 2 mL of methanol. After stirring an additional 2 min, the reaction mixture was poured into a 125-mL separatory funnel containing 30 mL of dichloromethane and 30 mL of an aqueous 3% HCl solution. The organic phase was separated, washed with two 30-mL portions of aqueous 3% HCl solution and 30 mL of brine, dried over magnesium sulfate, filtered through a small pad of neutral alumina, and concentrated to provide 0.203 g of a green oil. Column chromatography on 15 g of silica gel (elution with 20% ethyl acetate-hexanes) afforded 0.111 g (39%) of 1-acetoxy-6-cyanoazulene as a green solid, mp 112.0-113.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) : 8.16 (d, J = 10.0 Hz, 1H), 8.14 (d, J = 9.5 Hz, 1H), 8.01 (d, J = 4.3 Hz, 1H), 7.38 (d, J = 4.3 Hz, 1H), 7.26 (d, J = 9.5 Hz, 1H), 7.18 (d, J = 10.0 Hz, 1H), and 2.44 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) :	168.6, 140.0, 136.7, 136.1, 132.2, 130.9, 126.4, 125.4, 123.3, 120.8, 120.6, 116.9, and 20.9.	
IR (CCl_4) :	3010, 2930, 2190, 1765, 1575, 1480, 1415, 1380, 1355, 1300, 1250, 1185, and 1015 cm^{-1}.	
UV-Vis max (methanol) :	662 (ε = 342) and 283 (86,600) nm.	
Elemental Analysis :	Calculated for $C_{13}H_9NO_2$:	C, 73.92; H, 4.29; N, 6.63.
	Found :	C, 73.65; H, 4.04; N, 6.45.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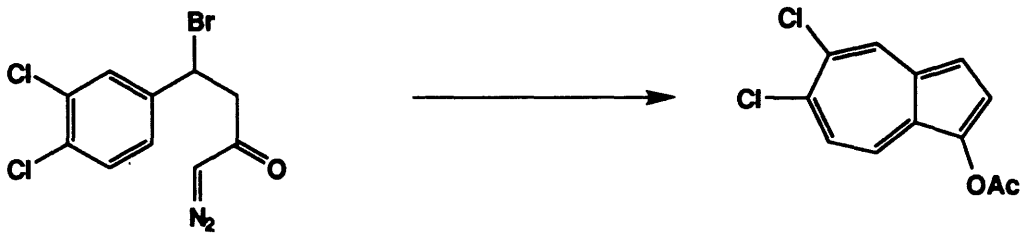
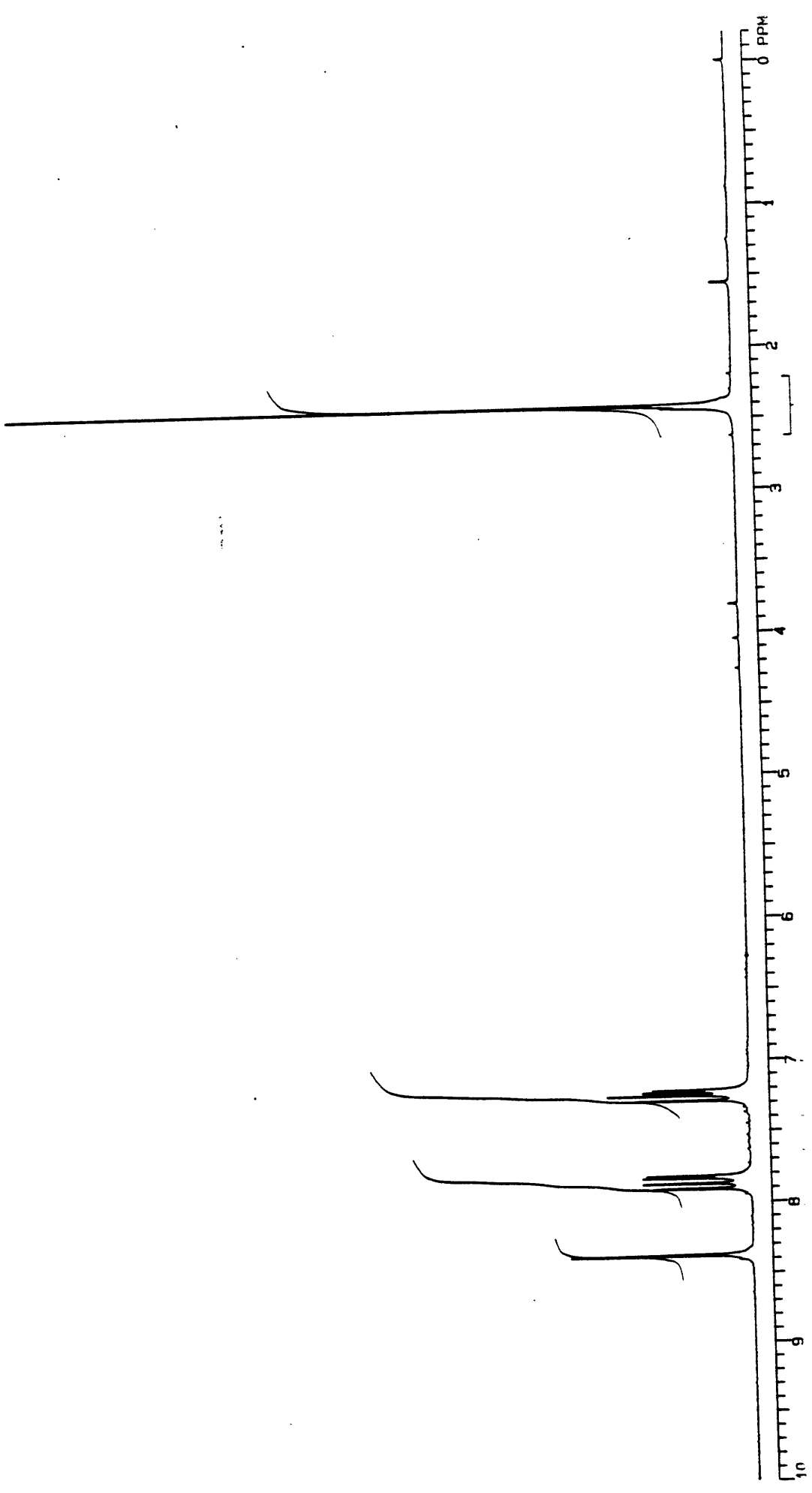


1-Acetoxy-5,6-dichloroazulene (264).

A 50-mL, three-necked, round-bottomed flask equipped with rubber septum, 15-mL pressure equalizing addition funnel, and an argon inlet adaptor was charged with rhodium pivalate (0.006 g, 0.0105 mmol) and 10 mL of dichloromethane. The addition funnel was charged with 4-bromo-4-(3,4-dichlorophenyl)-1-diazo-2-butanone (0.353 g, 1.10 mmol) and 8 mL of dichloromethane. The solution of the diazo ketone was added dropwise over 15 min to the rapidly stirred solution of the catalyst. The addition funnel was rinsed with 2 mL of dichloromethane, and the reaction mixture was stirred for 2 min. Acetic anhydride (0.561 g, 0.520 mL, 5.50 mmol) was added in one portion via syringe, and then 4-dimethylaminopyridine (0.403 g, 3.30 mmol) was immediately added in one portion. The resulting brown solution was stirred for 2 min and then treated with 2 mL of methanol. After stirring an additional 2 min, the reaction mixture was poured into a 125-mL separatory funnel containing 30 mL of dichloromethane and 30 mL of an aqueous 3% HCl solution. The organic phase was separated, washed with two 30-mL portions of aqueous 3% HCl solution and 30 mL of brine, dried over magnesium sulfate, filtered through a small pad of neutral alumina, and concentrated to provide 0.255 g of a blue-green oil. Column chromatography on 15 g of silica gel (elution with 5% ethyl acetate-hexanes) afforded 0.054 g (19%) of 1-acetoxy-5,6-dichloroazulene (contaminated with ca. 5% of 1-acetoxy-6,7-dichloroazulene) as a green solid, mp 73.0-76.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) : 8.37 (s, 1H), 7.89 (d, J = 11.0 Hz, 1H), 7.82 (d, J = 4.4 Hz, 1H), 7.27 (d, J = 11.0 Hz, 1H), 7.22 (d, J = 4.4 Hz, 1H), and 2.41 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) :	168.6, 142.7, 140.0, 137.3, 132.5, 130.3, 128.1, 126.6, 125.5, 121.8, 116.4, and 21.1.	
IR (CCl_4) :	3020, 2920, 1770, 1570, 1505, 1480, 1430, 1400, 1375, 1320, 1270, 1200, 1080, 1040, 995, 945, 910, 890, and 860 cm^{-1}.	
UV-Vis max (hexane) :	797 (ε = 110), 626 (320), 352 (7,780), and 287 (81,050) nm.	
Elemental Analysis :	Calculated for $C_{12}H_8Cl_2O_2$:	C, 56.50; H, 3.16.
	Found :	C, 56.24; H, 2.98.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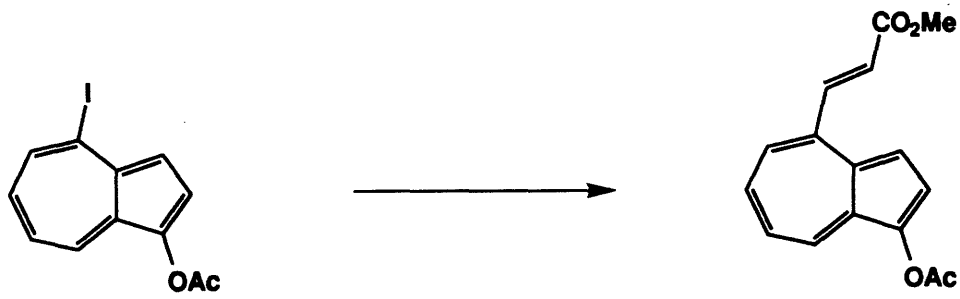
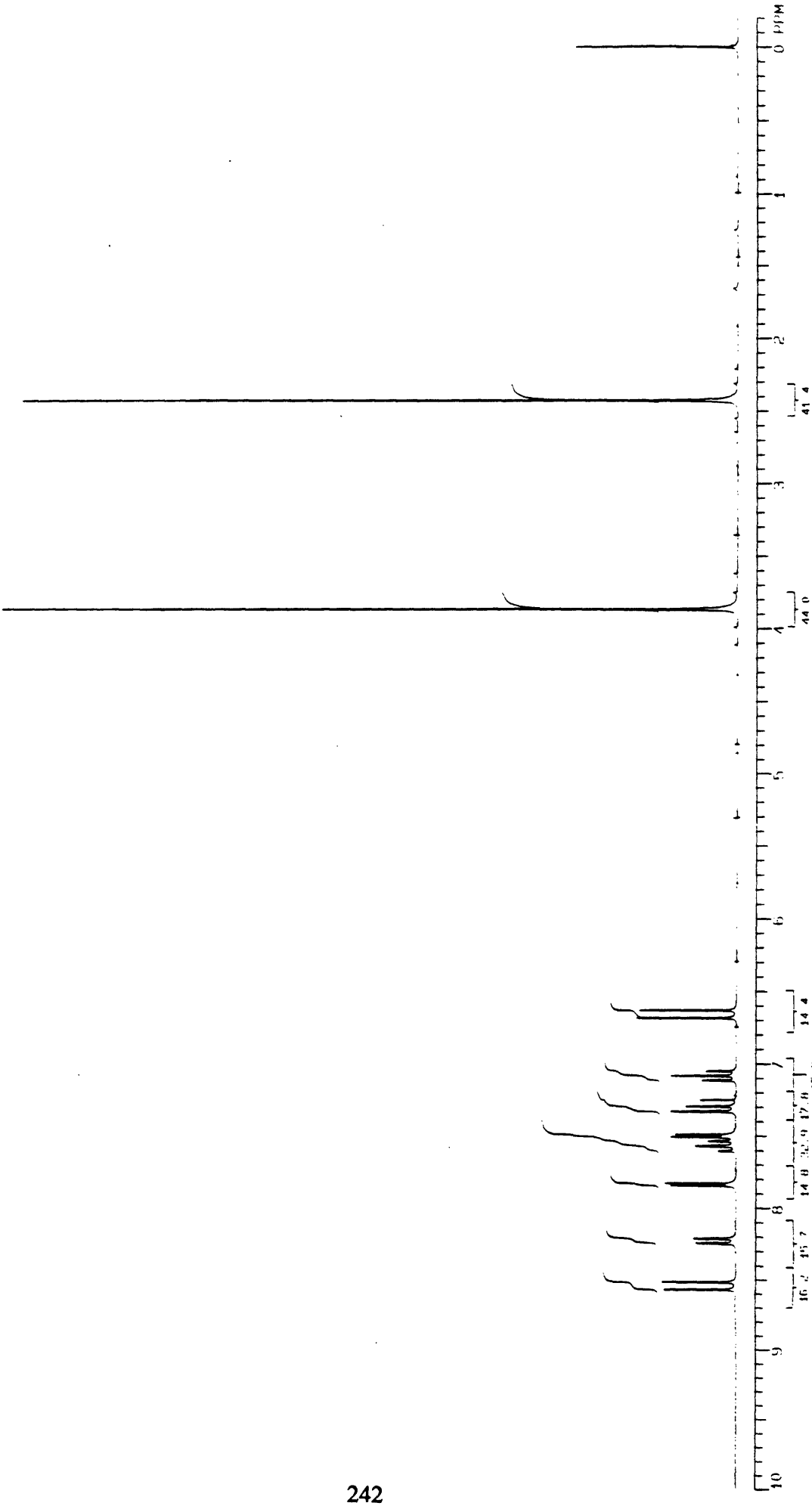


Methyl 3-[4-(1-acetoxyazulenyl)]acrylate (297).

A 50-mL, three-necked, round-bottomed flask equipped with rubber septum, glass stopper, and an argon inlet adaptor was charged with 1-acetoxy-4-iodoazulene (0.200 g, 0.641 mmol), tetrabutylammonium bromide (0.207 g, 0.641 mmol), sodium bicarbonate (0.134 g, 1.60 mmol), palladium acetate (0.014 g, 0.0641 mmol), and 5 mL of N,N-dimethylformamide. The reaction mixture was then treated with methyl acrylate (0.276 g, 0.300 mL, 3.20 mmol) and stirred at room temperature. After 20 h, an additional portion of palladium acetate (0.007 g, 0.032 mmol) was added. The reaction mixture stirred for 6 h, poured into 20 mL of water, and extracted with five 20-mL portions of diethyl ether. The combined organic phases were washed with 20 mL of water and 30 mL of brine, dried over magnesium sulfate, filtered, and concentrated to provide 0.137 g of a blue oil. Column chromatography on 30 g of silica gel (elution with 5% ethyl acetate-hexanes) afforded 0.136 g (79%) of methyl 3-[4-(1-acetoxyazulenyl)]acrylate as a green solid. An analytical sample was prepared by recrystallization from hexanes (-20 °C), mp 57.0-58.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) :	8.54 (d, J = 15.9 Hz, 1H), 8.23 (d, J = 9.1 Hz, 1H), 7.84 (d, J = 4.5 Hz, 1H), 7.57 (t, J = 10.5 Hz, 1H), 7.50 (d, J = 4.5 Hz, 1H), 7.31 (t, J = 10.5Hz, 1H), 7.08 (t, J = 9.6 Hz, 1H), 6.66 (d, J = 15.9 Hz, 1H), 3.87 (s, 3H), and 2.43 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) :	168.9, 166.6, 144.2, 141.6, 139.0, 137.3, 132.7, 132.3, 127.8, 127.1, 123.8, 121.9, 121.1, 111.2, 52.0, and 21.1.
IR (CCl_4) :	2940, 1760, 1720, 1540, 1430, 1400, 1365, 1305, 1295, 1200, 1160, 1040, and 1010 cm^{-1}.

UV-Vis max (hexane) :	649 (ε = 378), 352 (4,080), 292 (63,520), 257 (58,035), and 192 (6,505) nm.	
Elemental Analysis :	Calculated for $C_{16}H_{14}O_4$:	C, 71.10; H, 5.22.
	Found :	C, 70.97; H, 5.05.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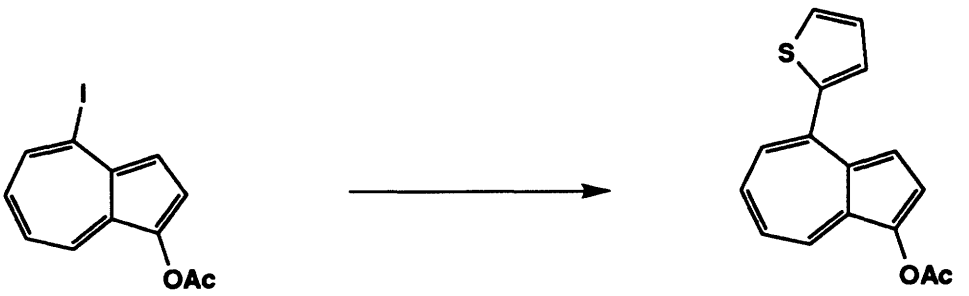

1-Acetoxy-4-(2-thienyl)azulene (298).

A 50-mL, three-necked, round-bottomed flask equipped with rubber septum, glass stopper, and an argon inlet adaptor was charged with 2-thienyllithium (1.0M in THF, 0.96 mL, 0.960 mmol) and 5 mL of tetrahydrofuran. The orange solution was then treated with zinc chloride (0.131 g, 0.961 mmol) and stirred 30 min. The greenish gray mixture was then treated with tris(dibenzylideneacetone)dipalladium (0.023 g, 0.0256 mmol) and triphenylarsine (0.031 g, 0.103 mmol). A 10-mL, one-necked, pear-shaped flask was charged with 1-acetoxy-4-iodoazulene (0.200 g, 0.641 mmol) and 4 mL of tetrahydrofuran. The azulene solution was transferred dropwise via cannula to reaction mixture over 1 min and the flask was rinsed with two 1.5-mL portions of tetrahydrofuran. After 30 min, the reaction mixture was poured into 30 mL of saturated ammonium chloride solution and 50 mL of diethyl ether. The phases were separated, and the organic phase was washed with 30 mL of saturated ammonium chloride solution and 30 mL of brine, dried over magnesium sulfate, filtered, and concentrated to provide 0.223 g of a greenish brown oil. Column chromatography on 20 g of silica gel (elution with 5% ethyl acetate-hexanes, compound applied adsorbed onto 0.500 g silica gel) afforded 0.140 g (81%) of 1-acetoxy-4-(2-thienyl)azulene as an olive green solid. An analytical sample was prepared by recrystallization from hexanes (-20 °C), mp 98.0-99.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) : 8.25 (d, J = 9.4 Hz, 1H), 7.76 (d, J = 4.6 Hz, 1H), 7.48-7.53 (m, 4 H), 7.28 (d, J = 10.6 Hz, 1H), 7.18 (dd, J = 3.8, 4.2 Hz, 1H), 7.04 (app t, J = 9.4, 9.8 Hz, 1H),

	and 2.44 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) :	169.3, 160.5, 144.0, 143.8, 138.9, 137.1, 132.6, 132.2, 128.4, 127.3, 127.1, 126.8, 126.2, 120.9, 114.4, and 21.1.
IR (CCl_4) :	3020, 2910, 1760, 1585, 1535, 1495, 1430, 1400, 1365 1315, 1205, 1040, and 900 cm^{-1}.
UV-Vis max (hexane) :	625 (ε = 438), 599 (377), 352 (4,725), 280 (28,350), and 239 (3,930) nm.
Elemental Analysis :	Calculated for $C_{16}H_{12}O_2S$: C, 71.62; H, 4.51. Found : C, 71.45; H, 4.59.

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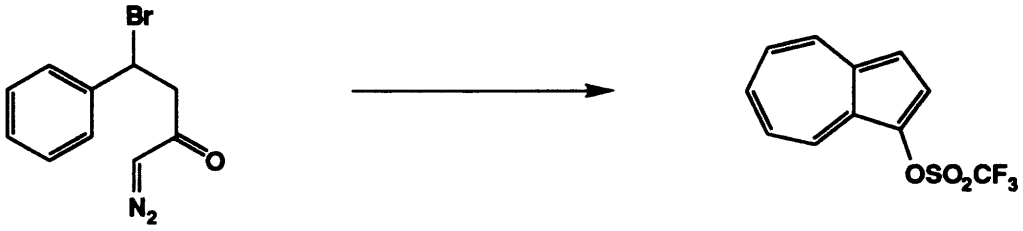
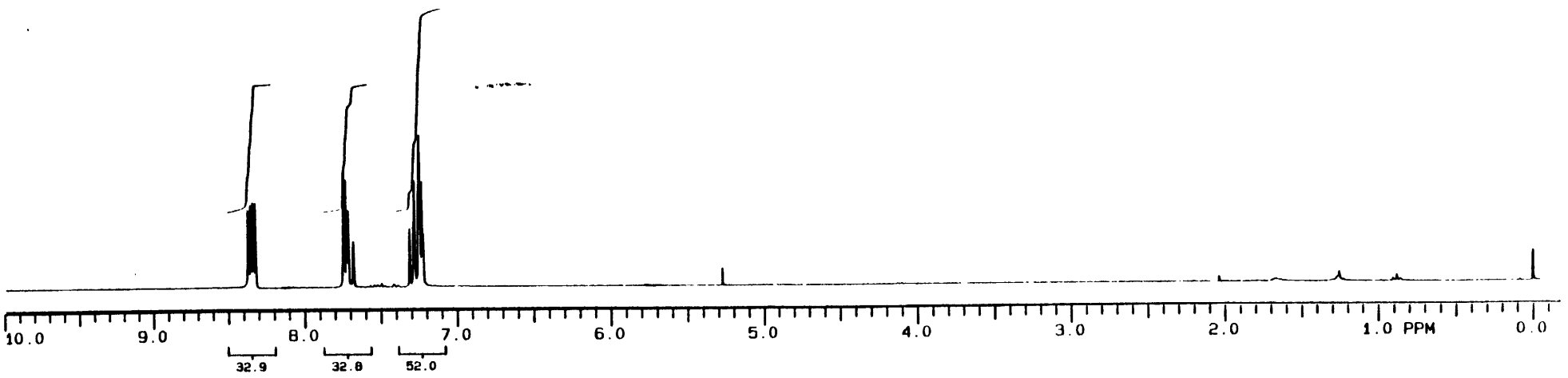


1-(Trifluoromethanesulfonyloxy)azulene (300).

A 250-mL, three-necked, round-bottomed flask equipped with rubber septum, 60-mL pressure equalizing addition funnel, and an argon inlet adaptor was charged with rhodium pivalate (0.0150 g, 0.0277 mmol) and 50 mL of dichloromethane. The addition funnel was charged with 4-bromo-1-diazo-3-phenyl-2-butanone (0.700 g, 2.77 mmol) and 45 mL of dichloromethane. The solution of the diazo ketone was added dropwise over 45 min to the rapidly stirred solution of the catalyst. The addition funnel was rinsed with 5 mL of dichloromethane, and the green reaction mixture was stirred for 3 min. N-phenyltrifluoromethanesulfonimide (0.988 g, 2.77 mmol) was added in one portion, and then 4-dimethylaminopyridine (1.01 g, 8.30 mmol, in 2 mL of dichloromethane) was immediately added in one portion. The resulting deep blue solution was stirred for 10 min and then treated with 2 mL of piperidine. After stirring an additional 15 min, the reaction mixture was poured into a 500-mL separatory funnel containing 100 mL of diethyl ether and 100 mL of an aqueous 3% HCl solution. The organic phase was separated, washed with two 100-mL portions of aqueous 3% HCl solution and 100 mL of brine, dried over magnesium sulfate, filtered through a small pad of neutral alumina, and concentrated to a black oil. Column chromatography on 50 g of silica gel (elution with 5% ethyl acetate-hexanes) afforded 1-(trifluoromethanesulfonyloxy)azulene as an unstable purple-blue oil. This material was used immediately in the next reaction.

^{1}H NMR (300 MHz, CDCl3) : 8.35 (d, J = 9.7Hz, 1H), 8.34 (d, J = 9.4 Hz, 1H), 7.68-7.74 (m, 2H), and 7.22-7.31 (m, 3H).

^{13}C NMR (75 MHz, CDCl3) :	139.7, 139.6, 136.1, 134.5, 132.5, 127.2, 126.7, 124.4, 124.1, 116.8, and 113.7.
IR (CCl_4) :	3000, 1580, 1550, 1490, 1420, 1400, 1310, 1240, 1210, 1140, 990, and 885 cm^{-1}.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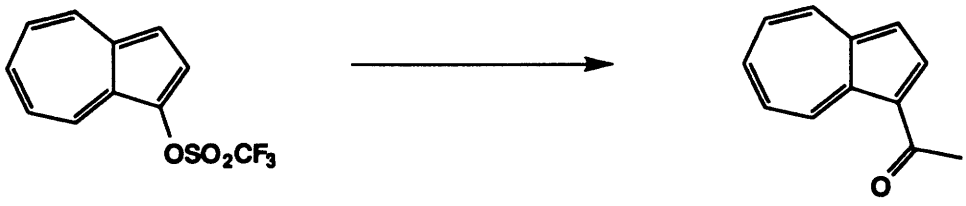
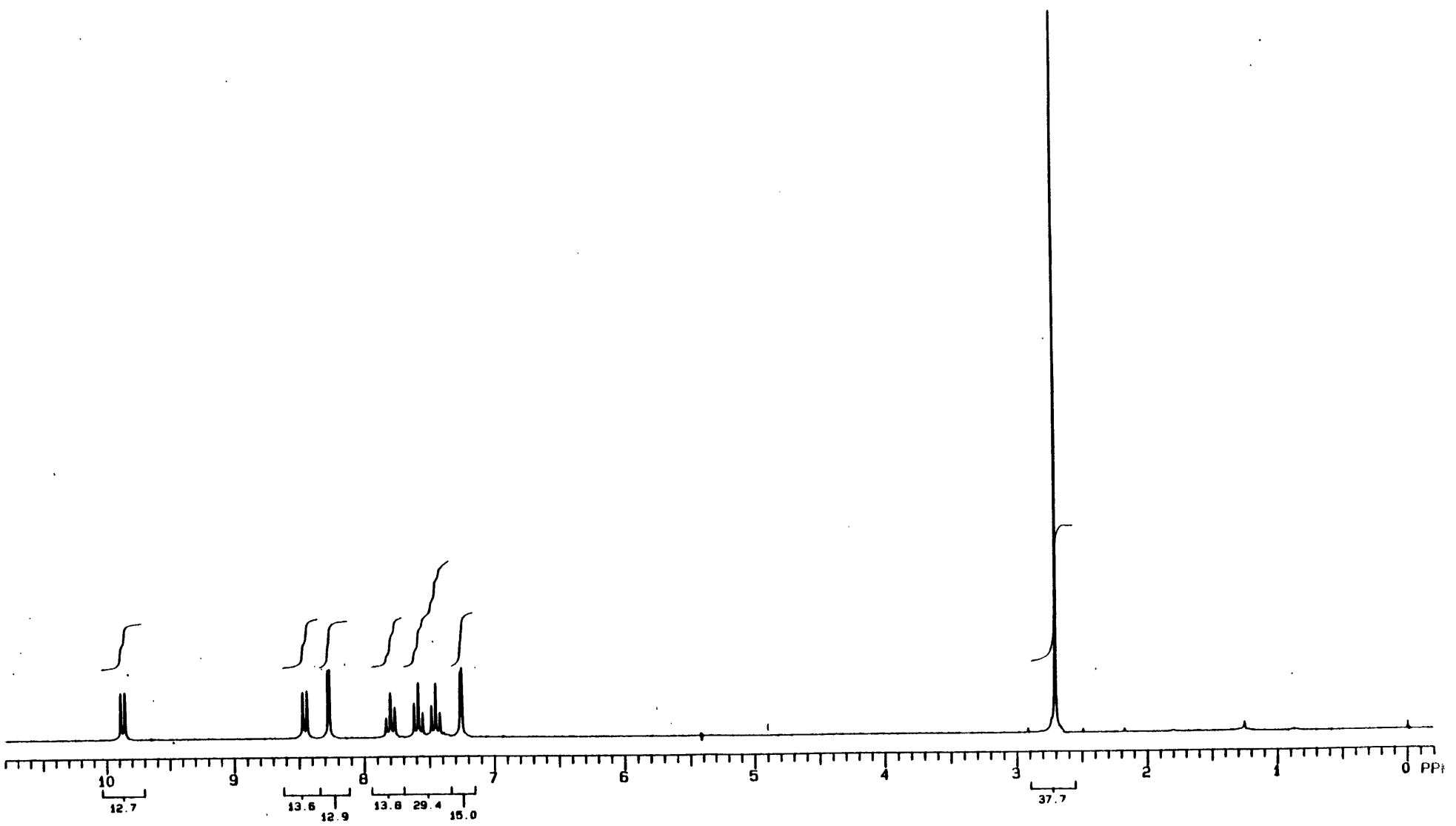


1-Acetylazulene (313).

A 50-mL, three-necked, round-bottomed flask equipped with rubber septum, glass stopper, and an argon inlet adaptor was charged with 1-(trifluoromethanesulfonyloxy)azulene and 7 mL of N-methylpyrrolidinone. The blue solution was then treated with lithium chloride (0.352 g, 8.30 mmol), tris(dibenzylideneacetone)dipalladium (0.101 g, 0.111 mmol) and triphenylarsine (0.136 g, 0.443 mmol). After 2 min, 1-ethoxy-1(trimethylstannyl)ethylene (0.974 g, 0.78 mL, 4.15 mmol) and two crystals of BHT were added to the reaction mixture. The reaction mixture was then stirred at room temperature for 2.5 h, poured into 50 mL of water and extracted with five-20 mL portions of pentane. The combined organic phases were washed with two 50-mL portions of 3% aqueous HCl solution and 75 mL of brine, dried over magnesium sulfate, filtered, and concentrated to provide 0.460 g of a purple oil. Column chromatography on 40 g of silica gel (elution with 5% ethyl acetate-hexanes, compound applied adsorbed onto 1.5 g silica gel) afforded 0.160 g (34% from 4-bromo-1-diazo-3-phenyl-2-butanone) of 1-acetylazulene[142] as a purple oil.

^{1}H NMR (300 MHz, $CDCl_3$) :	9.87 (d, J = 9.5 Hz, 1H), 8.45 (d, J = 9.7 Hz, 1H), 8.27 (d, J = 3.8 Hz, 1H), 7.80 (t, J = 9.8 Hz, 1H), 7.59 (t, J = 9.8 Hz, 1H), 7.45 (t, J = 9.7 Hz, 1H), 7.25 (d, J = 3.8 Hz, 1H), and 2.70 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) :	190.2, 145.1, 140.6, 140.1, 139.6, 139.5, 138.6, 129.3, 127.3, 125.2, 117.7, and 29.1.
IR (thin film) :	300, 2900, 1635, 1585, 1570, 1540, 1490, 1455, 1400, 1345, 1320, 1280, 1220, 1140, 1050, 1015, 985, 910, 865, 780, and 740 cm^{-1}.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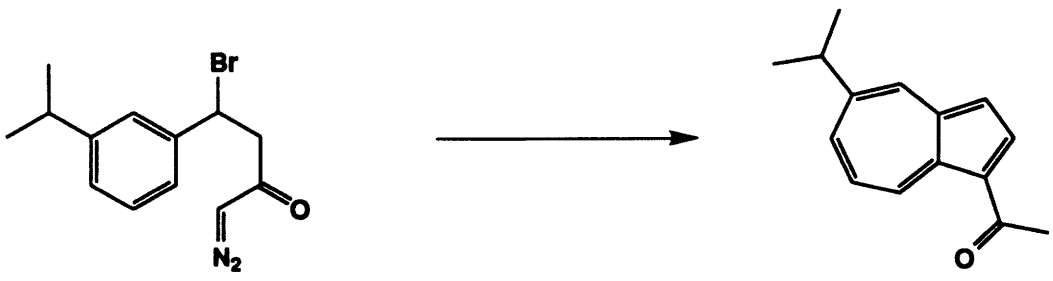

1-Acetyl-5-isopropylazulene (330).

A 250-mL, three-necked, round-bottomed flask equipped with rubber septum, 60-mL pressure equalizing addition funnel, and an argon inlet adaptor was charged with rhodium pivalate (0.0170 g, 0.0280 mmol) and 40 mL of diethyl ether. The addition funnel was charged with 4-bromo-1-diazo-4-(3-isopropylphenyl)-2-butanone (0.413 g, 1.39 mmol) and 30 mL of diethyl ether. The solution of the diazo ketone was added dropwise over 45 min to the rapidly stirred solution of the catalyst. The addition funnel was rinsed with 5 mL of diethyl ether, and the green reaction mixture was stirred for 10 min. N-phenyltrifluoromethanesulfonimide (0.500 g, 1.39 mmol) was added in one portion, and then 4-dimethylaminopyridine (0.513 g, 4.20 mmol, in 2 mL of dichloromethane) was immediately added in one portion. The resulting deep purple suspension was stirred for 15 min and then treated with 2 mL of piperidine. After stirring an additional 15 min, the reaction mixture was poured into a 500-mL separatory funnel containing 100 mL of diethyl ether and 100 mL of an aqueous 3% HCl solution. The organic phase was separated, washed with two 100-mL portions of aqueous 3% HCl solution and 100 mL of brine, dried over magnesium sulfate, filtered through a small pad of neutral alumina, and concentrated to a black oil. Column chromatography on 50 g of silica gel (elution with 5% ethyl acetate-hexanes) afforded 5-isopropyl-1-(trifluoromethanesulfonyloxy)azulene as an unstable blue oil.

A 50-mL, three-necked, round-bottomed flask equipped with rubber septum, glass stopper, and an argon inlet adaptor was charged with 5-isopropyl-1-(trifluoromethanesulfonyloxy)azulene and 8 mL of *N*-methylpyrrolidinone. The blue solution was then treated with lithium chloride (0.178 g, 4.20 mmol), tris(dibenzylideneacetone)-dipalladium (0.102 g, 0.112 mmol) and triphenylarsine (0.137 g, 0.448 mmol). After 2 min, 1-ethoxy-1(trimethylstannyl)ethylene (0.493 g, 0.40 mL, 2.10 mmol) and two crystals of BHT were added to the reaction mixture. The reaction mixture was then stirred at room temperature for 4.5 h, poured into 70 mL of water and extracted with five 20-mL portions of pentane. The combined organic phases were washed with two 50-mL portions of 10% aqueous HCl solution and 75 mL of brine, dried over magnesium sulfate, filtered, and concentrated to provide 0.327 g of a brown oil. Column chromatography on 60 g of silica gel (elution with 5% ethyl acetate-hexanes, compound applied adsorbed onto 1 g of silica gel) afforded 0.0380 g (13% from 4-bromo-1-diazo-4-(3-isopropylphenyl)-2-butanone) of 1-acetyl-5-isopropylazulene as a purple solid, mp 70.5-71.5 °C.

^{1}H NMR (300 MHz, $CDCl_3$) :	9.78 (d, J = 9.7 Hz, 1H), 8.43 (d, J = 2.0 Hz, 1H), 8.25 (d, J = 4.3 Hz, 1H), 7.77 (d, J = 10.7 Hz, 1H), 7.57 (t, J = 10.2 Hz, 1H), 7.18 (t, J = 4.3 Hz, 1H), 3.17 (sept, J = 6.8 Hz, 1H), 2.70 (s, 3H), and 1.39 (d, J = 6.8 Hz, 6H).
^{13}C NMR (75 MHz, $CDCl_3$) :	195.2, 148.3, 145.1, 140.6, 140.0, 138.8, 138.1, 138.0, 129.2, 124.2, 117.0, 38.6, 29.0, and 24.5.
IR (CCl_4) :	2950, 1635, 1540, 1490, 1455, 1410, 1390, 1220, 1140, 995, 890, and 870 cm^{-1}.
UV-Vis max (hexane) :	661 (ε = 200), 598 (525), 551 (605), 384 (13,030), 370 (12,440), 350 (6,615), 304 (46,605), 295 (40,780), 222 (23,750), and 192 (28,090) nm.
Elemental Analysis :	Calculated for $C_{15}H_{16}O$: C, 84.87; H, 7.59. Found : C, 84.80; H, 7.70.

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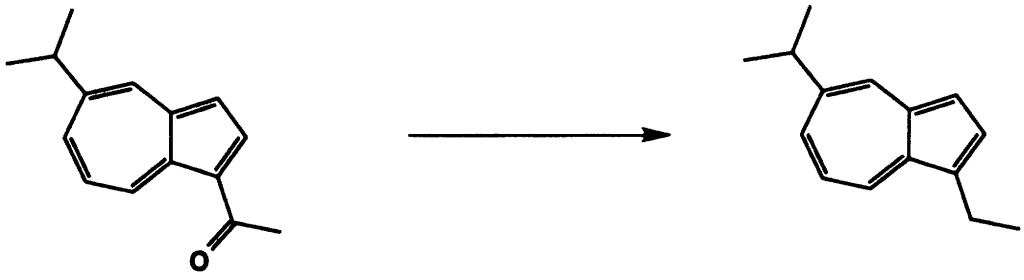
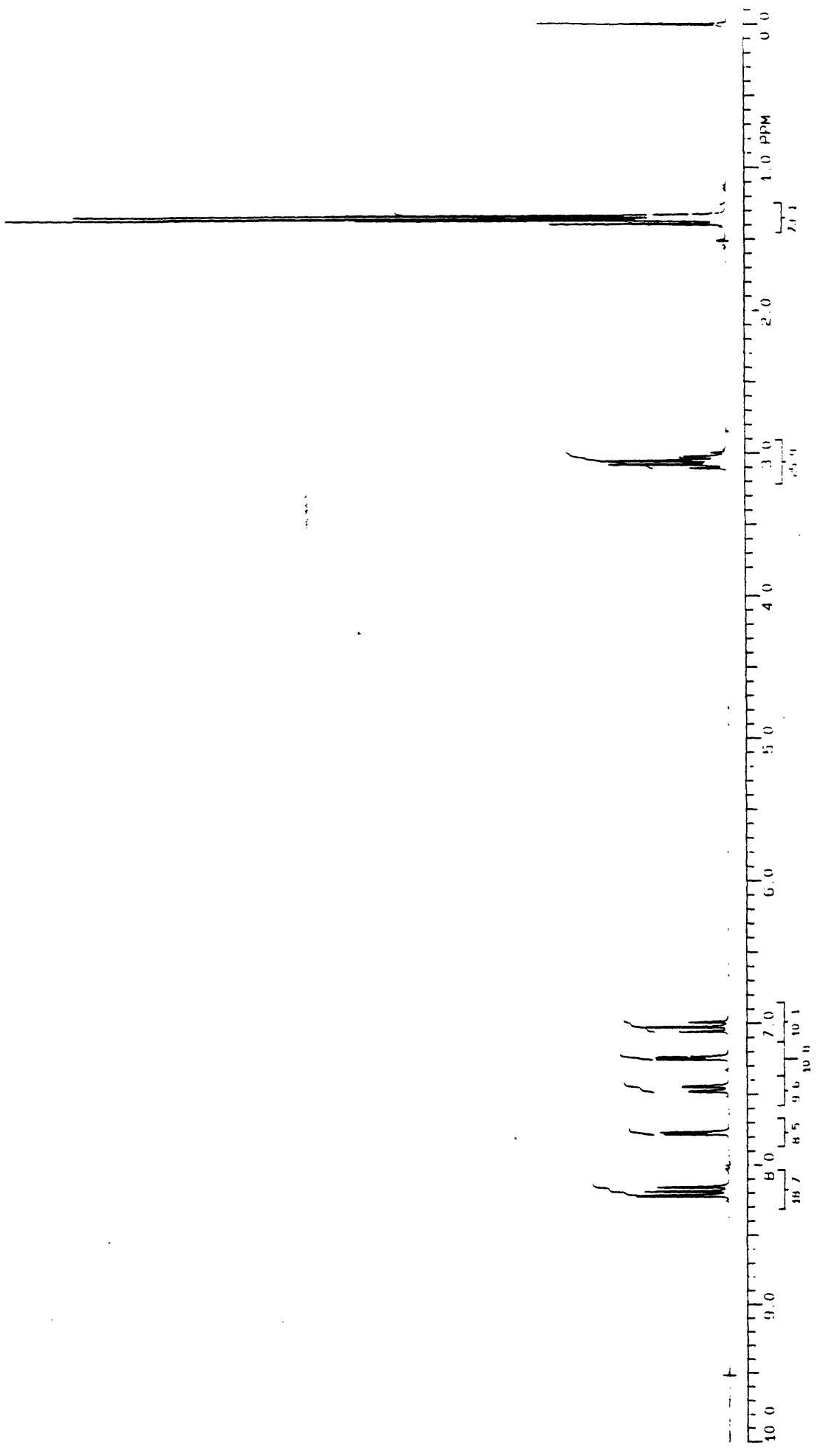


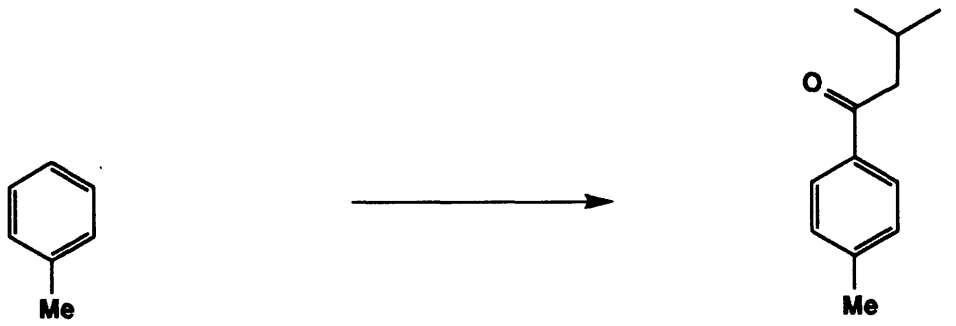
1-Ethyl-5-isopropylazulene (323).

A 50-mL, three-necked, round-bottomed flask equipped with rubber septum, 15-mL pressure equalizing addition funnel, and an argon inlet adaptor was charged with sodium borohydride (0.190 g, 5.04 mmol) and 5 mL of diglyme and cooled to 0 °C. The addition funnel was charged with 1-acetyl-5-isopropylazulene (0.033 g, 0.155 mmol), 4 mL of diethyl ether, and boron trifluoride etherate (1.09 g, 0.95 mL, 7.75 mmol). The resulting orange suspension was then added dropwise over 10 min to the sodium borohydride suspension. The addition funnel was rinsed with two 2.5-mL portions of diethyl ether, and the blue reaction mixture was stirred at 0 °C. After 1 h, the reaction mixture was poured into 50 mL of water and 20 mL of hexane. The phases were separated, and the aqueous phase was extracted with two 20-mL portions of hexane. The combined organic phases were washed with 30 mL of brine, dried over magnesium sulfate, filtered, and concentrated to provide 0.016 g of a blue oil. Column chromatography on 10 g of silica gel (elution with hexanes) afforded 0.012 g (39%) of 1-ethyl-5-isopropylazulene as a blue oil.

^{1}H NMR (300 MHz, $CDCl_3$) :	8.21 (d, J = 1.9 Hz, 1H), 8.17 (d, J = 9.6 Hz, 1H), 7.77 (d, J = 3.8 Hz, 1H), 7.43-7.48 (m, 1H), 7.24 (d, J = 3.8 Hz, 1H), 7.02 (app t, J = 10.0 Hz, 1H), 3.02-3.10 (m, 3H), and 1.33-1.39 (m, 9H).
^{13}C NMR (75 MHz, $CDCl_3$) :	141.8, 140.5, 136.2, 136.1, 136.0, 134.7, 131.9, 131.8, 120.8, 115.7, 38.3, 24.5, 20.4, and 15.8.

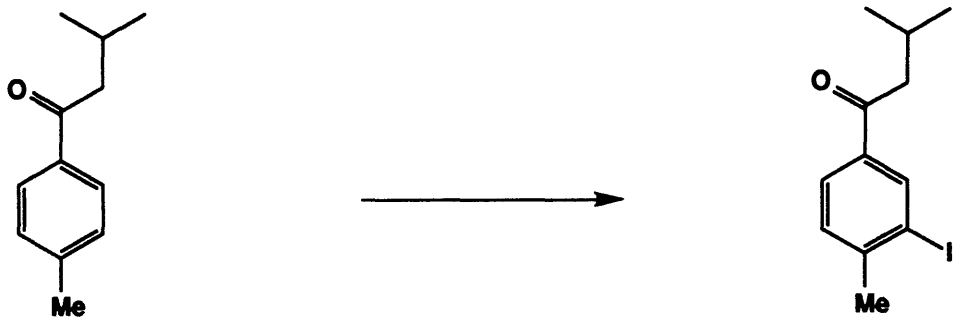
IR (thin film) : 2950, 2920, 2860, 1570, 1505, 1455, 1390, 1290, 1185, 1050, 905, and 760 cm^{-1}.





3-Methyl-1-(4-methylphenyl)-1-butanone (389).

A 250-mL, three-necked, round-bottomed flask equipped with a powder addition funnel, a glass stopper, and an argon inlet adaptor was charged with toluene (21.8 g, 25.0 mL, 236 mmol), isovaleryl chloride (15.0 g, 15.1 mL, 124 mmol) and 90 mL of carbon disulfide. The reaction mixture was cooled to 0 °C while aluminum(III) chloride (30.0 g, 225 mmol) was added in small portions via the addition funnel over 45 min. The addition funnel was replaced with a reflux condensor, and the orange-brown reaction mixture was heated to 45 °C. After 30 min, the brown reaction mixture was allowed to cool to room temperature and then was poured into 50 mL of con HCl and 50 mL of ice water. The phases were separated and the aqueous phase was extracted with three 75-mL portions of diethyl ether. The combined organic phases were washed with 200 mL of brine, dried over magnesium sulfate, filtered, and concentrated to provide 26.4 g of an orange oil. Vacuum distillation of this material using a short path condensor and 4" Vigreux column afforded 18.2 g (83%) of 3-methyl-1-(4-methylphenyl)-1-butanone as a clear oil (bp 115-120 °C @ 1 mmHg) with spetral charateristcs identical to those previously reported for this compound.[186]

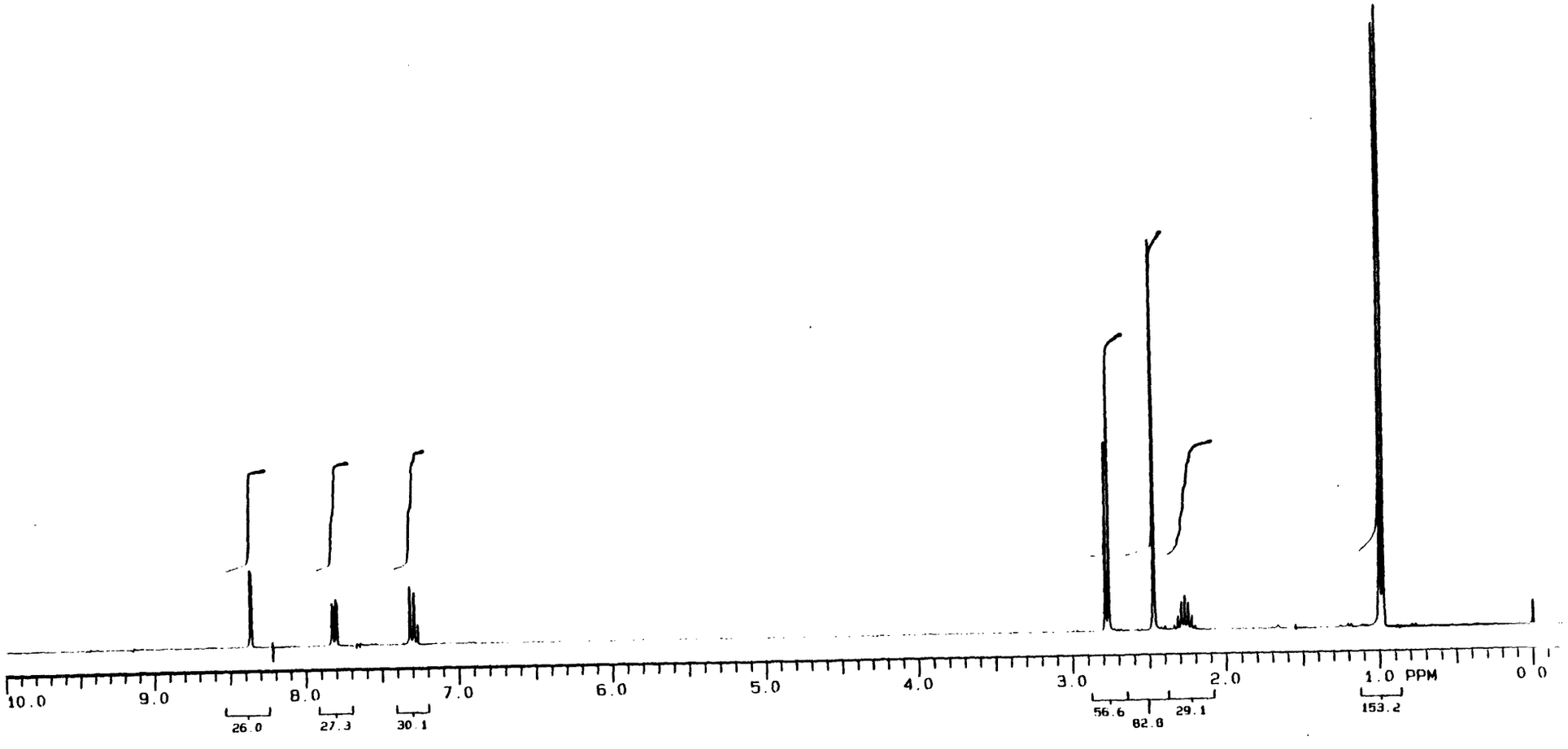


3-Methyl-1-(3-iodo-4-methylphenyl)-1-butanone (390).

A 250-mL, three-necked, round-bottomed flask equipped with rubber septum, a glass stopper, and an argon inlet adaptor was charged with 3-methyl-1-(4-methylphenyl)-1-butanone (1.02 g, 5.79 mmol) and 100 mL of dichloromethane. Iodine (III) tris(trifluoroacetate) (2.69 g, 5.79 mmol) was then added in one portion, and the resulting orange solution was stirred at room temperature. After 18 h, 100 mL of 20% aqueous sodium iodide solution was added, resulting in a dark brown solution. After 30 min, the reaction mixture was poured into 100 mL of saturated sodium bicarbonate solution, and the phases were separated. The aqueous phases was extracted with two 50-mL portions of dichloromethane. The combined organic phases were washed with 100 mL of 5% aqueous sodium thiosulfate solution and 200 mL of brine, dried over magnesium sulfate, filtered, and concentrated to provide 1.61 g of a yellow oil. Column chromatography on 40 g of silica gel (elution with benzene) afforded 1.34 g (77%) of 3-methyl-1-(3-iodo-4-methylphenyl)-1-butanone as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) :	8.36 (d, J = 1.9 Hz, 1H), 7.81 (dd, J = 1.9, 7.9 Hz, 1H), 7.30 (d, J = 7.9 Hz, 1H), 2.78 (d, J = 6.5 Hz, 2H), 2.47 (s, 3H), 2.27 (app sept, J = 6.7 Hz, 1H), and 0.99 (d, J = 6.7 Hz, 6H).
^{13}C NMR (75 MHz, $CDCl_3$) :	198.3, 146.7, 138.8, 136.7, 129.7, 127.8, 101.1, 47.4, 28.3, 25.1, and 22.7.

IR (thin film) : 2960, 1680, 1595, 1550, 1460, 1380, 1295, 1200, 1030, and 910 cm^{-1}.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82.8
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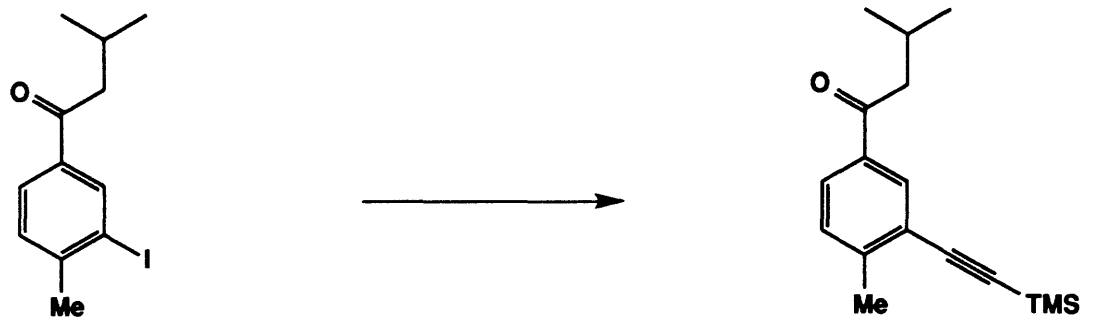
153.2

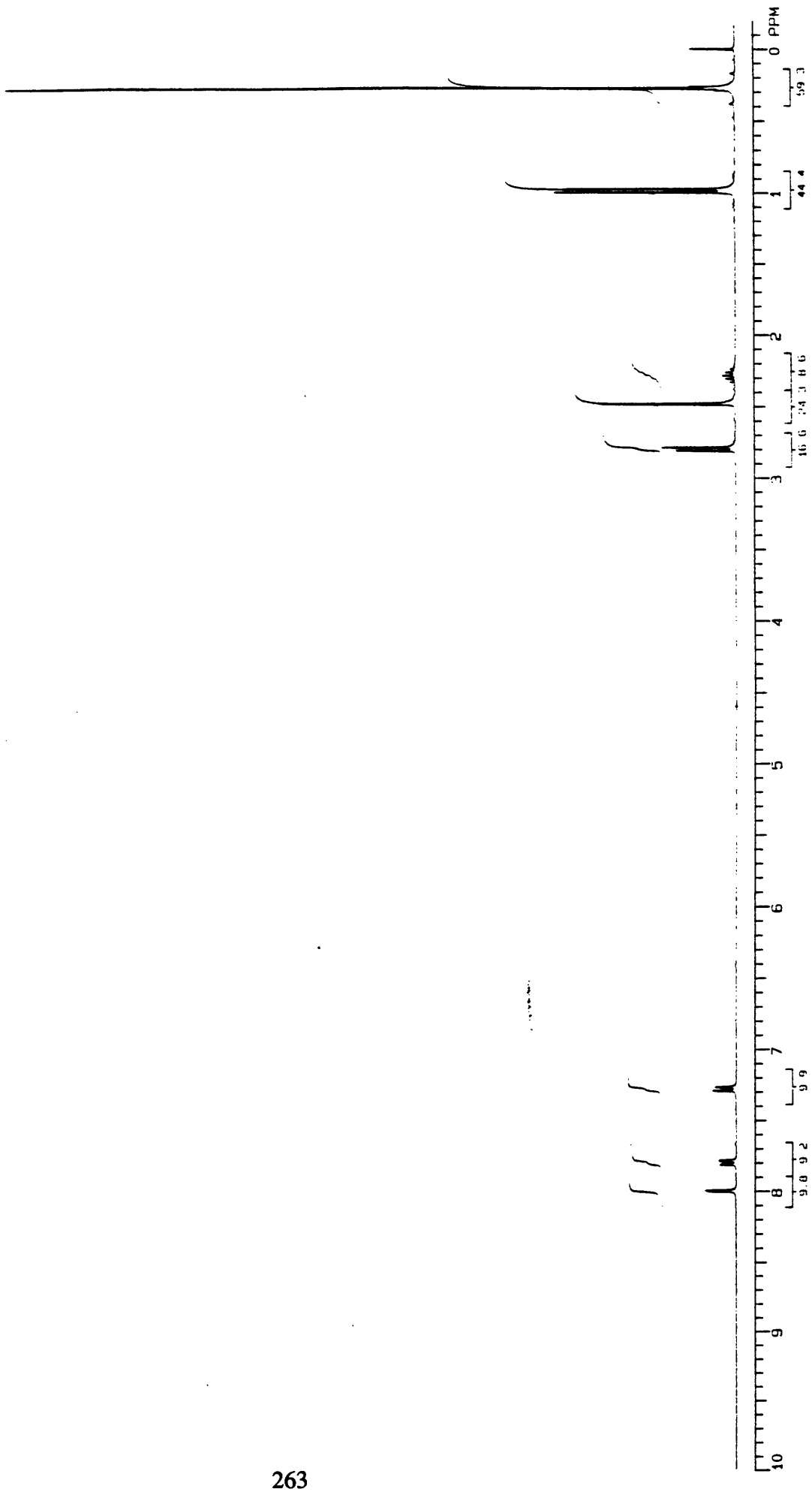


3-Methyl-1-[4-methyl-3-(2-trimethylsilylethynyl)phenyl]-1-butanone (388).

A 50-mL, three-necked, round-bottomed flask equipped with rubber septum, a glass stopper, and an argon inlet adaptor was charged with 3-methyl-1-(3-iodo-4-methylphenyl)-1-butanone (1.29 g, 4.26 mmol), bis(triphenylphosphine)palladium(II) chloride (0.060 g, 0.0852 mmol), copper(I) iodide (0.008 g, 0.0426 mmol), and 20 mL of diethylamine. After 2 min, (trimethylsilyl)acetylene (0.627 g, 0.90 mL, 6.39 mmol) was added in one portion via syringe, and the reaction mixture was stirred at room temperature. After 2.5 h, the reaction mixture was concentrated. The residue was dissolved in 25 mL of methylene chloride and washed with two 20-mL portions of water and 50 mL of brine, dried over magnesium sulfate, filtered, and concentrated to provide 1.37 g of a yellow oil. Column chromatography on 20 g of silica gel (elution with 20% ethyl acetate in hexanes) afforded 1.17 g (100%) of 3-methyl-1-[4-methyl-3-(2-trimethylsilylethynyl)phenyl]-1-butanone as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) :	8.00 (d, J = 1.8 Hz, 1H), 7.80 (dd, J = 1.8, 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 2.80 (d, J = 6.9 Hz, 2H), 2.48 (s, 3H), 2.28 (app sept, J = 6.8 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H), and 0.28 (s, 9H).
^{13}C NMR (75 MHz, $CDCl_3$) :	199.0, 145.7, 135.0 131.9, 129.6, 127.9, 123.3, 102.9, 99.3, 47.3, 25.0, 22.7, and 0.08.

IR (thin film) : 2955, 2150, 1675, 1600, 1560, 1450, 1400, 1375, 1300, 1250, 1210, 1170, 1110, 900, 845, and 760 cm^{-1}.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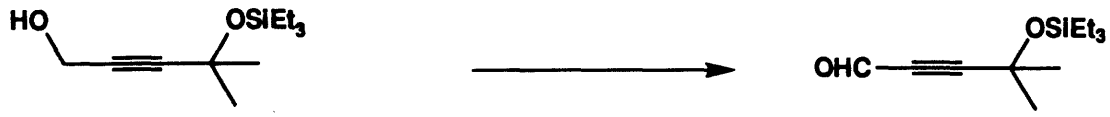
4-Methyl-4-(triethylsilyloxy)-2-pentyn-1-ol (396).

A 250-mL, three-necked, round-bottomed flask equipped with rubber septum, a glass stopper, and an argon inlet adaptor was charged with 2-methyl-2-(triethylsilyloxy)-3-butyne[217] (4.00 g, 20.2 mmol) and 100 mL of tetrahydrofuran. The reaction mixture was cooled to -30 °C while n-BuLi solution (2.52 M in hexanes, 11.2 mL, 28.2 mmol) was added dropwise via syringe over 5 min. The resulting yellow reaction mixture was stirred at -30 °C for 30 min and then treated with paraformaldehyde (0.848 g, 28.2 mmol). The cooling bath was removed and the reaction mixture was allowed to warm to room temperature. After 4.5 h, the reaction mixture was poured into 40 mL of aqueous 10% HCl solution and 170 mL of diethyl ether. The phases were separated, and the organic phase was washed with 100 mL of brine, dried over magnesium sulfate, filtered, and concentrated to provide 4.68 g of a yellow oil. Vacuum distillation of this material using a short path condensor and 4" Vigreux column afforded 3.27 g (71%) of 4-methyl-4-(triethylsilyloxy)-2-pentyn-1-ol as a clear oil (bp 95 °C @ 0.4 mmHg).

IR (thin film) : 3320, 2940, 2860, 1455, 1410, 1370, 1340, 1240, 1160, 1035, 1000, 895, and 730 cm^{-1}.

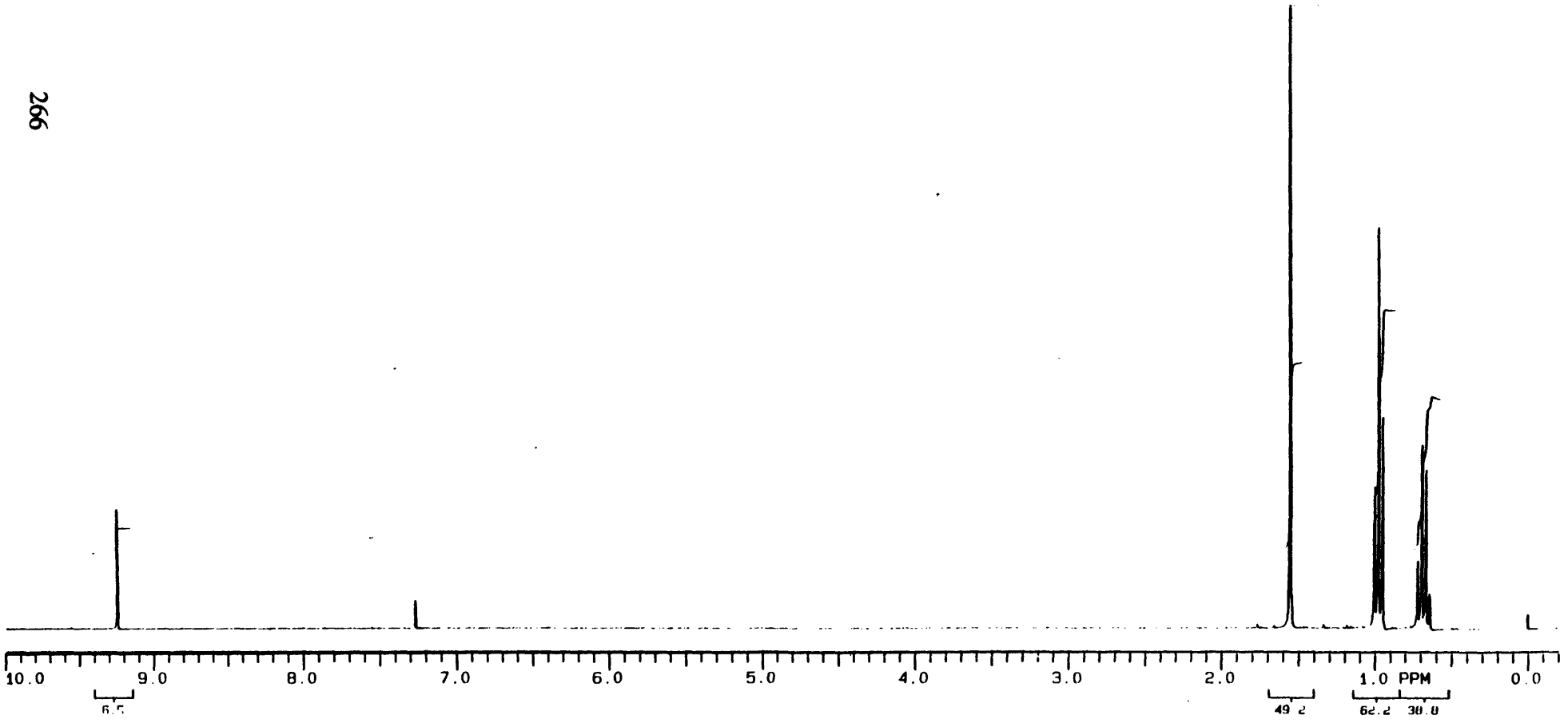
[217]This material was produced in 51% yield by silylation of 2-methyl-3-butyn-2-ol (Et_3SiCl, Et_3N, DMAP, CH_2Cl_2). For a previous synthesis of this compound, see ref. 195.



4-Methyl-4-(triethylsilyloxy)-2-pentyn-1-al (398).

A 50-mL, three-necked, round-bottomed flask equipped with a 10-mL addition funnel, a glass stopper, and an argon inlet adaptor was charged with ethylmagnesium bromide (3.0 M in diethyl ether, 1.2 mL, 3.60 mmol) and 4 mL of tetrahydrofuran. The addition funnel was charged with *t*-butanol (0.267 g, 0.34 mL, 3.60 mmol) and 1 mL of tetrahydrofuran. The alcohol solution was added dropwise to the Grignard reagent over 3 min, and the addition funnel was rinsed with 1 mL of tetrahydrofuran. The addition funnel was then charged with 4-methyl-4-(triethylsilyloxy)-2-pentyn-1-ol (0.685 g, 3.00 mmol) and 7 mLof tetrahydrofuran. The alcohol solution was then added dropwise to the reaction mixture over 5 min, and the addition funnel was rinsed with 2 mL of tetrahydrofuran. After 5 min, the reaction mixture was treated with 1,1'-(azodicarbonyl)piperidine (0.908 g, 3.60 mmol) in 6 mL of tetrahydrofuran (added dropwise via the addition funnel over 10 min), and the orange reaction mixture was stirred at room temperature. After 2.5 h, the reaction mixture was poured into 15 mL of brine. The phases were separated and the aqueous phase was extracted with three 10-mL portions of diethyl ether. The combined organic phases were washed with 25 mL of saturated sodium bicarbonate solution and 25 mL of brine, dried over magnesium sulfate, filtered twice, and concentrated to provide a white paste. Column chromatography on 30 g of silica gel (elution with 5% ethyl acetate in hexanes) afforded 0.463 g (69%) of 4-methyl-4-(triethylsilyloxy)-2-pentyn-1-al as a clear oil.

^{1}H NMR (300 MHz, $CDCl_3$) : 9.25 (s, 1H), 1.55 (s, 6H), 0.97 (t, J = 7.7 Hz, 9H), and 0.78 (q, J = 7.7 Hz, 6H).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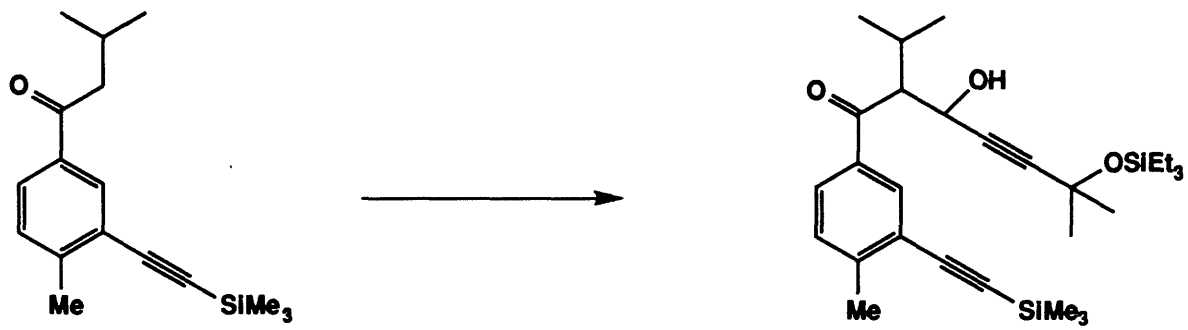
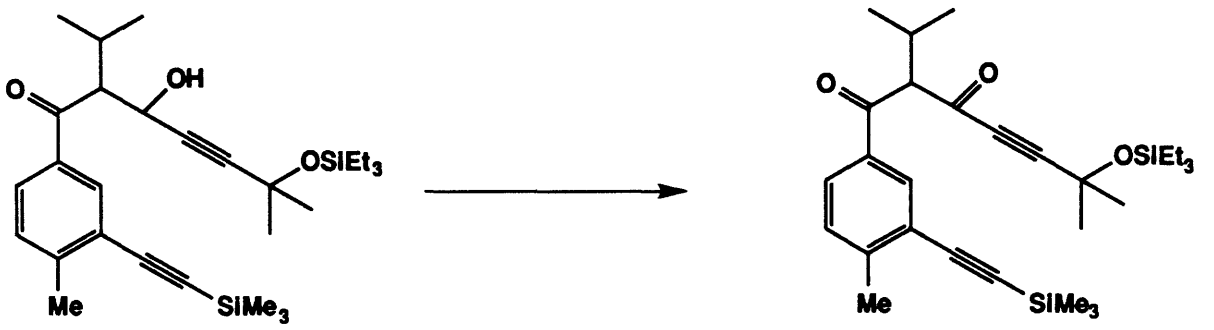


Aldol Product (414).

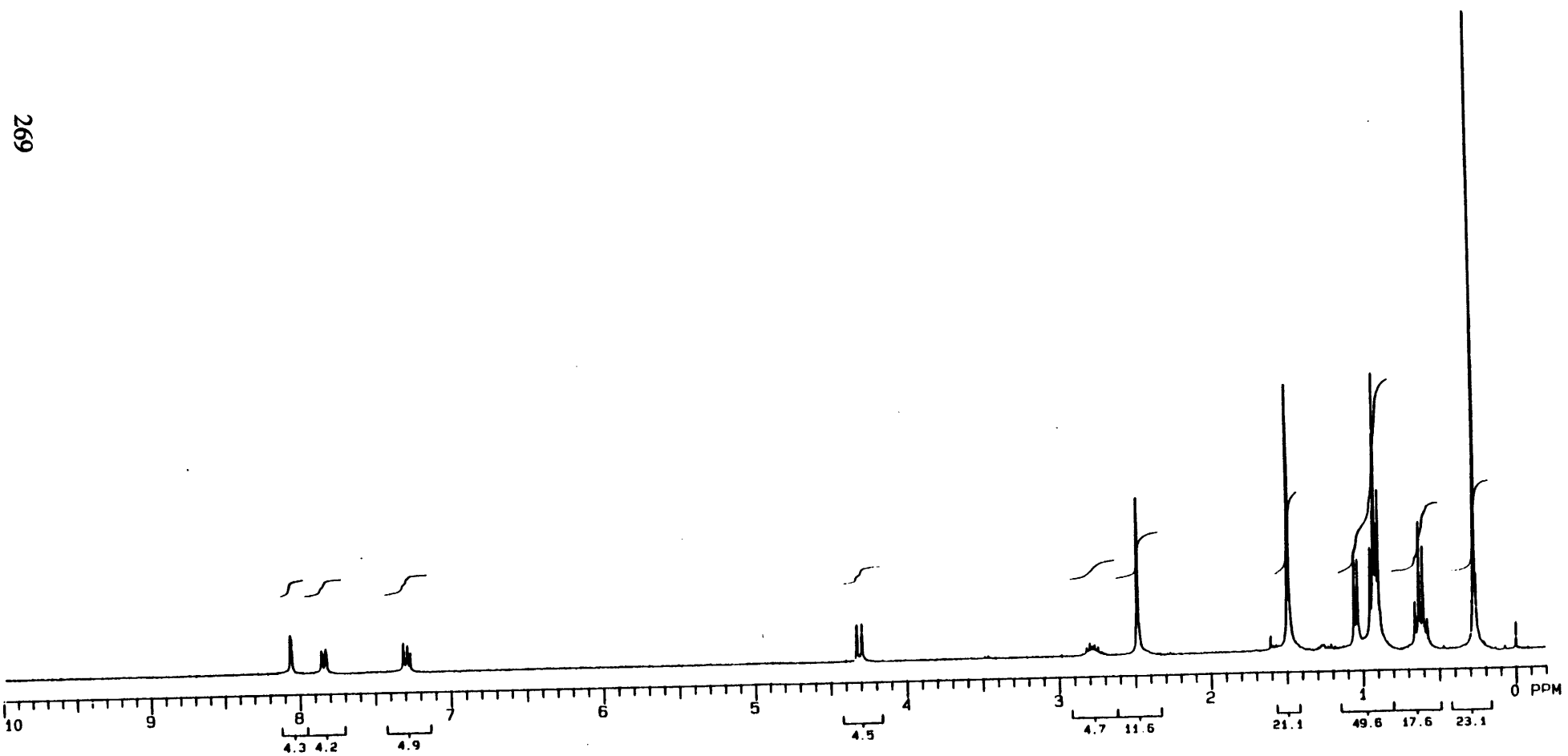
A 50-mL, three-necked, round-bottomed flask equipped with a 10-mL addition funnel, a glass stopper, and an argon inlet adaptor was charged with 1,1,1,3,3,3-hexamethyldisilazane (0.284 g, 0.37 mL, 1.76 mmol) and 6 mL of tetrahydrofuran. The reaction mixture was cooled to 0 °C and treated dropwise over 2 min with *n*-BuLi solution (2.53 M in hexanes, 0.64 mL, 1.61 mmol). After 5 min, the reaction mixture was cooled to -78 °C and stirred for an additional 5 min. The addition funnel was charged with 3-methyl-1-[4-methyl-3-(2-trimethylsilylethynyl)phenyl]-1-butanone (0.400 g, 1.47 mmol) and 6 mL of tetrahydrofuran. The ketone solution was added dropwise to the LiHMDS solution over 15 min, and the addition funnel was rinsed with 2 mL of tetrahydrofuran. After 30 min, the reaction mixture was treated dropwise over 5 min with 4-methyl-4-(triethylsilyloxy)-2-pentyn-1-al (0.372 g, 1.64 mmol) in 5 mL of tetrahydrofuran (precooled to -78 °C). After 30 min, the reaction mixture was poured into 30 mL of saturated ammonium chloride solution and 50 mL of diethyl ether. The phases were separated, and the aqueous phase was extracted with two 10-mL portions of diethyl ether. The combined organic phases were washed with 30 mL of brine, dried over magnesium sulfate, filtered, and concentrated to provide 0.806 g of a yellow oil. Column chromatography on 30 g of silica gel (elution with 5% ethyl acetate in hexanes) afforded 0.542 g (74%) of **414** as a clear oil. This material was used without further purification in the next reaction.



1,3-Diketone (417).

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and an argon inlet adaptor was charged with **414** (0.282 g, 0.565 mmol) and 10 mL of dichloromethane. The reaction mixture was treated with the Dess-Martin periodinane (0.350 g, 0.825 mmol) and stirred at room temperature. After 1.25 h, the cloudy reaction mixture was filtered through a small plug of silica gel, and the filtrate was concentrated to provide 0.446 g of a white paste. Column chromatography on 20 g of silica gel (elution with 5% ethyl acetate in hexanes) afforded 0.239 g (85%) of **417** as a clear oil.

^{1}H NMR (300 MHz, $CDCl_3$) :	8.05 (d, J = 1.9 Hz, 1H), 7.84 (dd, J = 1.9, 8.2 Hz, 1H), 7.30 (d, J = 8.2 Hz, 1H), 4.31 (d, J = 9.9 Hz, 1H), 2.77-2.80 (m, 1H), 2.49 (s, 3H), 1.49 (s, 6H), 1.04 (d, J = 6.7 Hz, 3H), 0.86-1.02 (m, 12H), 0.57-0.66 (m, 6H), and 0.27 (s, 9H).
^{13}C NMR (75 MHz, $CDCl_3$) :	192.8, 182.6, 146.6, 134.9, 132.4, 129.8, 128.4, 123.7, 121.6, 99.8, 99.6, 80.8, 71.1, 66.2, 32.3, 29.5, 21.0, 20.6, 7.0, 6.0, and 0.1.
IR (thin film) :	2950, 2860, 2200, 2120, 1685, 1655, 1590, 1455, 1400, 1245, 1160, 1035, 1000, 895, 840, and 730 cm^{-1}.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